



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/CA99/00114  <b>(22) International Filing Date:</b> 17 February 1999 (17.02.99)  <b>(30) Priority Data:</b> 60/075,425                      20 February 1998 (20.02.98)                      US  <b>(71) Applicant (for all designated States except US):</b> BIOCHEM VACCINS INC. [CA/CA]; 2323 boulevard du Parc Technologique, Sainte-Foy, Québec G1P 4R8 (CA).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BRODEUR, Bernard, R. [CA/CA]; 2401 rue Maritain, Sillery, Québec G1T 1N6 (CA). RIOUX, Clément [CA/CA]; 1012 Jean-Charles Cantin, Ville de Cap Rouge, Québec G1Y 2X1 (CA). BOYER, Martine [CA/CA]; Apt. 204, 25 des Mouettes, Beauport, Québec G1E 7G1 (CA). CHARLEBOIS, Isabelle [CA/CA]; 410 Mirabel, St-Nicolas, Québec G7A 2L5 (CA). HAMEL, Josée [CA/CA]; 2401 rue Maritain, Sillery, Québec G1T 1N6 (CA). MARTIN, Denis [CA/CA]; 4728-G rue Gaboury, St-Augustin-de-Desmaures, Québec G3A 1E9 (CA).		<b>(74) Agents:</b> CÔTE, France et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montréal, Québec H3A 2Y3 (CA).  <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> GROUP B STREPTOCOCCUS ANTIGENS		
<b>(57) Abstract</b>  Group B streptococcus (GBS) proteins and polynucleotides encoding them are disclosed. Said proteins are antigenic and therefore useful vaccine components for the prophylaxis or therapy of streptococcus infection in animals. Also disclosed are recombinant methods of producing the protein antigens as well as diagnostic assays for detecting streptococcus bacterial infection.		

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## GROUP B STREPTOCOCCUS ANTIGENS

5

## FIELD OF THE INVENTION

The present invention is related to antigens, more particularly protein antigens of group B streptococcus (GBS) bacterial pathogen which are useful as vaccine components for therapy and/or prophylaxis.

## 15 BACKGROUND OF THE INVENTION

15

Streptococcus are gram (+) bacteria that are differentiated by group specific carbohydrate antigens A through O found on their cell surface. Streptococcus groups are further distinguished by type-specific capsular polysaccharide antigens. Several serotypes have been identified for the Group B streptococcus (GBS) : Ia, Ib, II, III, IV, V, VI, VII and VIII. GBS also contains antigenic proteins known as "C-proteins" (alpha, beta, gamma and delta), some of which have been cloned.

25

Although GBS is a common component of the normal human vaginal and colonic flora this pathogen has long been recognized as a major cause of neonatal sepsis and meningitis, late-onset meningitis in infants, postpartum endometritis as well as mastitis in dairy herds. Expectant mothers exposed to GBS are at risk of postpartum infection and may transfer the infection to their baby as the child passes through the birth canal. Although the organism is sensitive to antibiotics, the high attack rate and rapid onset of sepsis in neonates and meningitis in infants results in high morbidity and mortality.

35

To find a vaccine that will protect individuals from GBS infection, researches have turned to the type-specific antigens. Unfortunately these polysaccharides have proven to  
5 be poorly immunogenic in humans and are restricted to the particular serotype from which the polysaccharide originates. Further, capsular polysaccharide elicit a T cell independent response i.e. no IgG production. Consequently capsular polysaccharide antigens are unsuitable  
10 as a vaccine component for protection against GBS infection.

Others have focused on the C-protein beta antigen which demonstrated immunogenic properties in mice and rabbit models. This protein was found to be unsuitable as a human  
15 vaccine because of its undesirable property of interacting with high affinity and in a non-immunogenic manner with the Fc region of human IgA. The C-protein alpha antigen is rare in type III serotypes of GBS which is the serotype responsible for most GBS mediated conditions and is  
20 therefore of little use as a vaccine component.

Therefore there remains an unmet need for GBS antigens that may be used as vaccine components for the prophylaxis and/or  
25 therapy of GBS infection.

#### SUMMARY OF THE INVENTION

30 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence selected from the group consisting of:

SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5,  
35 SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10,  
SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15,  
SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19,

SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24,  
SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29,  
SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34,  
SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39,  
5 SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments,  
analogous or derivatives thereof.

In other aspects, there is provided vectors comprising  
polynucleotides of the invention operably linked to an  
10 expression control region, as well as host cells transfected  
with said vectors and methods of producing polypeptides  
comprising culturing said host cells under conditions  
suitable for expression.

15 In yet another aspect, there is provided novel polypeptides  
encoded by polynucleotides of the invention.

#### BRIEF DESCRIPTION OF THE DRAWINGS

20 Figure 1a is the DNA sequence of clone 1 (SEQ ID NO :1) with  
corresponding amino acid sequences for open reading frames;  
figure 1b is the amino acid sequence SEQ ID NO: 2;  
figure 1c is the amino acid sequence SEQ ID NO: 3;  
25 figure 1d is the amino acid sequence SEQ ID NO: 4;  
figure 1e is the amino acid sequence SEQ ID NO: 5;  
figure 1f is the amino acid sequence SEQ ID NO: 6;

Figure 2a is the DNA sequence of clone 2 (SEQ ID NO :7) with  
30 corresponding amino acid sequences for open reading frames;  
figure 2b is the amino acid sequence SEQ ID NO: 8;  
figure 2c is the amino acid sequence SEQ ID NO: 9;  
figure 2d is the amino acid sequence SEQ ID NO:10;  
figure 2e is the amino acid sequence SEQ ID NO:11;  
35 figure 2f is the amino acid sequence SEQ ID NO:12;

Figure 3a is the DNA sequence of clone 3 (SEQ ID NO :13) with corresponding amino acid sequences for open reading frames;

figure 3b is the amino acid sequence SEQ ID NO:14;

5 figure 3c is the amino acid sequence SEQ ID NO:15;

figure 3d is the amino acid sequence SEQ ID NO:16;

figure 3e is the amino acid sequence SEQ ID NO:17;

figure 3f is the amino acid sequence SEQ ID NO:18;

figure 3g is the amino acid sequence SEQ ID NO:19;

10 figure 3h is the amino acid sequence SEQ ID NO:20;

figure 3i is the amino acid sequence SEQ ID NO:21;

Figure 4a is the DNA sequence of clone 4 (SEQ ID NO :22) with corresponding amino acid sequences for open reading frames;

15 figure 4b is the amino acid sequence SEQ ID NO:23;

figure 4c is the amino acid sequence SEQ ID NO:24;

figure 4d is the amino acid sequence SEQ ID NO:25;

20 figure 4e is the amino acid sequence SEQ ID NO:26;

Figure 5a is the DNA sequence of clone 5 (SEQ ID NO :27) with corresponding amino acid sequences for open reading frames;

figure 5b is the amino acid sequence SEQ ID NO:28;

25 figure 5c is the amino acid sequence SEQ ID NO:29;

figure 5d is the amino acid sequence SEQ ID NO:30;

figure 5e is the amino acid sequence SEQ ID NO:31;

Figure 6a is the DNA sequence of clone 6 (SEQ ID NO :32) ;

30 figure 6b is the amino acid sequence SEQ ID NO:33;

figure 6c is the amino acid sequence SEQ ID NO:34;

figure 6d is the amino acid sequence SEQ ID NO:35;

figure 6e is the amino acid sequence SEQ ID NO:36;

35 Figure 7a is the DNA sequence of clone 7 (SEQ ID NO :37);

figure 7b is the amino acid sequence SEQ ID NO:38;

figure 7c is the amino acid sequence SEQ ID NO:39;

figure 7d is the amino acid sequence SEQ ID NO:40;

figure 7e is the amino acid sequence SEQ ID NO:41;

- 5 Figure 8 is the DNA sequence of a part of clone 7 including a signal sequence (SEQ ID NO :42);

Figure 9 is the DNA sequence of a part of clone 7 without a signal sequence (SEQ ID NO :43);

- 10 Figure 9a is the amino acid sequence (SEQ ID NO:44);

Figure 10 represents the distribution of anti-GBS ELISA titers in sera from CD-1 mice immunized with recombinant GBS protein corresponding to the SEQ ID NO:39.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel antigenic polypeptides of group B streptococcus (GBS) characterized by the amino acid sequence selected from the group consisting of:

SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5,  
SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10,  
SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15,  
10 SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19,  
SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24,  
SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29,  
SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34,  
SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39,  
15 SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments,  
analogues or derivatives thereof.

A preferred embodiment of the invention includes SEQ ID NO :39 and SEQ ID NO:44.

20 A further preferred embodiment of the invention is SEQ ID NO :39.

A further preferred embodiment of the invention is SEQ ID NO :44.

25 As used herein, "fragments", "derivatives" or "analogues" of the polypeptides of the invention include those polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably conserved) and which may be natural or unnatural.

30 The terms «fragments», «derivatives» or «analogues» of polypeptides of the present invention also include polypeptides which are modified by addition, deletion,



substitution of amino acids provided that the polypeptides retain the capacity to induce an immune response.

- By the term «conserved amino acid» is meant a substitution of one or more amino acids for another in which the antigenic determinant (including its secondary structure and hydropathic nature) of a given antigen is completely or partially conserved in spite of the substitution.
- For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity, which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.
- Preferably, derivatives and analogs of polypeptides of the invention will have about 70% identity with those sequences illustrated in the figures or fragments thereof. That is, 70% of the residues are the same. More preferably polypeptides will have greater than 95% homology. In another preferred embodiment, derivatives and analogs of polypeptides of the invention will have fewer than about 20 amino acid residue substitutions, modifications or deletions and more preferably less than 10. Preferred substitutions are those known in the art as conserved i.e. the substituted residues share physical or chemical properties such as hydrophobicity, size, charge or functional groups.

Furthermore, in those situations where amino acid regions are found to be polymorphic, it may be desirable to vary one or more particular amino acids to more effectively mimic the  
5 different epitopes of the different GBS strains.

Also included are polypeptides which have fused thereto other compounds which alter the polypeptides biological or pharmacological properties i.e. polyethylene glycol (PEG) to  
10 increase half-life; leader or secretory amino acid sequences for ease of purification; prepro- and pro- sequences; and (poly)saccharides.

Moreover, the polypeptides of the present invention can be  
15 modified by terminal  $-NH_2$  acylation (eg. by acetylation, or thioglycolic acid amidation, terminal carboxy amidation, e.g. with ammonia or methylamine) to provide stability, increased hydrophobicity for linking or binding to a support or other molecule.

20 Also contemplated are hetero and homo polypeptide multimers of the polypeptide fragments, analogues and derivatives. These polymeric forms include, for example, one or more polypeptides that have been cross-linked with cross-linkers  
25 such as avidin/biotin, gluteraldehyde or dimethyl-superimide. Such polymeric forms also include polypeptides containing two or more tandem or inverted contiguous sequences, produced from multicistronic mRNAs generated by recombinant DNA technology.

30 Preferably, a fragment, analog or derivative of a polypeptide of the invention will comprise at least one antigenic region i.e. at least one epitope.

In order to achieve the formation of antigenic polymers  
35 (i.e. synthetic multimers), polypeptides may be utilized having bishaloacetyl groups, nitroarylhalides, or the like,

where the reagents being specific for thio groups.  
Therefore, the link between two mercapto groups of the  
different peptides may be a single bond or may be composed  
of a linking group of at least two, typically at least four,  
5 and not more than 16, but usually not more than about 14  
carbon atoms.

In a particular embodiment, polypeptide fragments, analogs  
and derivatives of the invention do not contain a methionine  
10 (Met) starting residue. Preferably, polypeptides will not  
incorporate a leader or secretory sequence (signal  
sequence). The signal portion of a polypeptide of the  
invention may be determined according to established  
molecular biological techniques. In general, the  
15 polypeptide of interest may be isolated from a GBS culture  
and subsequently sequenced to determine the initial residue  
of the mature protein and therefor the sequence of the  
mature polypeptide.

20 According to another aspect, there is provided vaccine  
compositions comprising one or more GBS polypeptides of the  
invention in admixture with a pharmaceutically acceptable  
carrier diluent or adjuvant.

25 Suitable adjuvants include oils i.e. Freund's complete or  
incomplete adjuvant; salts i.e.  $\text{AlK}(\text{SO}_4)_2$ ,  $\text{AlNa}(\text{SO}_4)_2$ ,  
 $\text{AlNH}_4(\text{SO}_4)_2$ ,  $\text{Al}(\text{OH})_3$ ,  $\text{AlPO}_4$ , silica, kaolin; saponin  
derivative; carbon polynucleotides i.e. poly IC and poly AU  
and also detoxified cholera toxin (CTB) and E.coli heat  
30 labile toxin for induction of mucosal immunity. Preferred  
adjuvants include QuilA<sup>TM</sup>, Alhydrogel<sup>TM</sup> and Adjuphos<sup>TM</sup>.  
Vaccines of the invention may be administered parenterally  
by injection, rapid infusion, nasopharyngeal absorption,  
dermoabsorption, or bucal or oral.

35

Vaccine compositions of the invention are used for the treatment or prophylaxis of *streptococcus* infection and/or diseases and symptoms mediated by *streptococcus* infection, in particular group A *streptococcus* (*pyogenes*), group B *streptococcus* (GBS or *agalactiae*), *dysgalactiae*, *uberis*, *nocardia* as well as *Staphylococcus aureus*. General information about *Streptococcus* is available in Manual of Clinical Microbiology by P.R.Murray et al. (1995, 6<sup>th</sup> Edition, ASM Press, Washington, D.C.). More particularly group B *streptococcus*, *agalactiae*. In a particular embodiment vaccines are administered to those individuals at risk of GBS infection such as pregnant women and infants for sepsis, meningitis and pneumonia as well as immunocompromised individuals such as those with diabetes, liver disease or cancer. Vaccines may also have veterinary applications such as for the treatment of mastitis in cattle which is mediated by the above mentioned bacteria as well as *E.coli*.

The vaccine of the present invention can also be used for the manufacture of a medicament used for the treatment or prophylaxis of *streptococcus* infection and/or diseases and symptoms mediated by *streptococcus* infection, in particular group A *streptococcus* (*pyogenes*), group B *streptococcus* (GBS or *agalactiae*), *dysgalactiae*, *uberis*, *nocardia* as well as *Staphylococcus aureus*. More particularly group B *streptococcus*, *agalactiae*.

Vaccine compositions are preferably in unit dosage form of about 0.001 to 100 µg/kg (antigen/body weight) and more preferably 0.01 to 10 µg/kg and most preferably 0.1 to 1 µg/kg 1 to 3 times with an interval of about 1 to 12 weeks intervals between immunizations, and more preferably 1 to 6

weeks.

According to another aspect, there is provided polynucleotides encoding polypeptides of group B

5 streptococcus (GBS) characterized by the amino acid sequence selected from the group consisting of:

SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5,  
 SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10,  
 SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15,  
 10 SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19,  
 SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24,  
 SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29,  
 SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34,  
 SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39,  
 15 SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments,  
 analogs or derivatives thereof.

Preferred polynucleotides are those illustrated in figures  
 1a (SEQ ID NO: 1), 2a (SEQ ID NO: 7), 3a (SEQ ID NO: 13), 4a  
 20 (SEQ ID NO: 22), 5a (SEQ ID NO: 27), 6a (SEQ ID NO: 32), 7a  
 (SEQ ID NO: 37), 8 (SEQ ID NO : 42) and 9 (SEQ ID NO : 43)  
 which correspond to the open reading frames, encoding  
 polypeptides of the invention.

25 Preferred polynucleotides are those illustrated in figures  
 1a (SEQ ID NO: 1), 2a (SEQ ID NO: 7), 3a (SEQ ID NO: 13), 4a  
 (SEQ ID NO: 22), 5a (SEQ ID NO: 27), 6a (SEQ ID NO: 32), 7a  
 (SEQ ID NO: 37), 8 (SEQ ID NO : 42) and 9 (SEQ ID NO : 43)  
 and fragments, analogues and derivatives thereof.

30 More preferred polynucleotides of the invention are those  
 illustrated in Figures 7 (SEQ ID NO : 37), 8 (SEQ ID NO :  
 42) and 9 (SEQ ID NO : 43).

35 Most preferred polynucleotides of the invention are those  
 illustrated in Figures 8 (SEQ ID NO : 42) and 9 (SEQ ID NO :

43) .

It will be appreciated that the polynucleotide sequences illustrated in the figures may be altered with degenerate  
5 codons yet still encode the polypeptides of the invention.

Due to the degeneracy of nucleotide coding sequences, other polynucleotide sequences which encode for substantially the same polypeptides of the present invention may be used in  
10 the practice of the present invention. These include but are not limited to nucleotide sequences which are altered by the substitution of different codons that encode the same amino acid residue within the sequence, thus producing a silent change.

15 Accordingly the present invention further provides polynucleotides which hybridize to the polynucleotide sequences herein above described (or the complement sequences thereof) having 50% and preferably at least 70%  
20 identity between sequences. More preferably polynucleotides are hybridizable under stringent conditions i.e. having at least 95% identity and most preferably more than 97% identity.

25 By capable of hybridizing under stringent conditions is meant annealing of a nucleic acid molecule to at least a region of a second nucleic acid sequence (whether as cDNA, mRNA, or genomic DNA) or to its complementary strand under standard conditions, e.g. high temperature and/or low salt  
30 content, which tend to disfavor hybridization of noncomplementary nucleotide sequences. A suitable protocol is described in Maniatis T. et al., Molecular cloning : A Laboratory Manual, Cold Springs Harbor Laboratory, 1982, which is herein incorporated by reference.

35 In a further aspect, polynucleotides encoding polypeptides

of the invention, or fragments, analogs or derivatives thereof, may be used in a DNA immunization method. That is, they can be incorporated into a vector which is replicable and expressible upon injection thereby producing  
5 the antigenic polypeptide in vivo. For example polynucleotides may be incorporated into a plasmid vector under the control of the CMV promoter which is functional in eukaryotic cells. Preferably the vector is injected intramuscularly.

10 According to another aspect, there is provided a process for producing polypeptides of the invention by recombinant techniques by expressing a polynucleotide encoding said polypeptide in a host cell and recovering the expressed  
15 polypeptide product. Alternatively, the polypeptides can be produced according to established synthetic chemical techniques i.e. solution phase or solid phase synthesis of oligopeptides which are ligated to produce the full polypeptide (block ligation).

20 For recombinant production, host cells are transfected with vectors which encode the polypeptide, and then cultured in a nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes.  
25 Suitable vectors are those that are viable and replicable in the chosen host and include chromosomal, non-chromosomal and synthetic DNA sequences e.g. bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA. The polypeptide  
30 sequence may be incorporated in the vector at the appropriate site using restriction enzymes such that it is operably linked to an expression control region comprising a promoter, ribosome binding site (consensus region or Shine-Dalgarno sequence), and optionally an operator (control  
35 element). One can select individual components of the expression control region that are appropriate for a given

host and vector according to established molecular biology principles (Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor, N.Y., 1989 incorporated herein by reference). Suitable promoters include but are not  
5 limited to LTR or SV40 promoter, *E.coli* lac, tac or trp promoters and the phage lambda P<sub>L</sub> promoter. Vectors will preferably incorporate an origin of replication as well as selection markers i.e. ampicillin resistance gene. Suitable bacterial vectors include pET, pQE70, pQE60, pQE-9, pbs,  
10 pD10 phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A, ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 and eukaryotic vectors pBlueBacIII, pWLNEO, pSV2CAT, pOG44, pXT1, pSG, pSVK3, pBPV, pMSG and pSVL. Host cells may be bacterial i.e. *E.coli*, *Bacillus subtilis*,  
15 *Streptomyces*; fungal i.e. *Aspergillus niger*, *Aspergillus nidulins*; yeast i.e. *Saccharomyces* or eukaryotic i.e. CHO, COS.

Upon expression of the polypeptide in culture, cells are  
20 typically harvested by centrifugation then disrupted by physical or chemical means (if the expressed polypeptide is not secreted into the media) and the resulting crude extract retained to isolate the polypeptide of interest. Purification of the polypeptide from culture media or lysate  
25 may be achieved by established techniques depending on the properties of the polypeptide i.e. using ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxylapatite  
30 chromatography and lectin chromatography. Final purification may be achieved using HPLC.

The polypeptide may be expressed with or without a leader or secretion sequence. In the former case the leader may be  
35 removed using post-translational processing (see US



4,431,739; 4,425,437; and 4,338,397 incorporated herein by reference) or be chemically removed subsequent to purifying the expressed polypeptide.

- 5 According to a further aspect, the GBS polypeptides of the invention may be used in a diagnostic test for streptococcus infection in particular GBS infection. Several diagnostic methods are possible, for example detecting streptococcus organism in a biological sample, the following procedure may
- 10 be followed:
- a) obtaining a biological sample from a patient;
  - b) incubating an antibody or fragment thereof reactive with a GBS polypeptide of the invention with the biological sample to form a mixture; and
  - 15 c) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence of streptococcus.

- Alternatively, a method for the detection of antibody
- 20 specific to a streptococcus antigen in a biological sample containing or suspected of containing said antibody may be performed as follows:
- a) isolating a biological sample from a patient;
  - b) incubating one or more GBS polypeptides of the invention or fragments thereof with the biological
  - 25 sample to form a mixture; and
  - c) detecting specifically bound antigen or bound fragment in the mixture which indicates the presence of antibody specific to streptococcus.

- 30 One of skill in the art will recognize that this diagnostic test may take several forms, including an immunological test such as an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay or a latex agglutination assay, essentially
- 35 to determine whether antibodies specific for the protein are present in an organism.

The DNA sequences encoding polypeptides of the invention may also be used to design DNA probes for use in detecting the presence of streptococcus in a biological sample suspected of containing such bacteria. The detection method of this invention comprises:

- a) isolating the biological sample from a patient;
- b) incubating one or more DNA probes having a DNA sequence encoding a polypeptide of the invention or fragments thereof with the biological sample to form a mixture; and
- c) detecting specifically bound DNA probe in the mixture which indicates the presence of streptococcus bacteria.

The DNA probes of this invention may also be used for detecting circulating streptococcus i.e. GBS nucleic acids in a sample, for example using a polymerase chain reaction, as a method of diagnosing streptococcus infections. The probe may be synthesized using conventional techniques and may be immobilized on a solid phase, or may be labeled with a detectable label. A preferred DNA probe for this application is an oligomer having a sequence complementary to at least about 6 contiguous nucleotides of the GBS polypeptides of the invention.

Another diagnostic method for the detection of streptococcus in a patient comprises:

- a) labeling an antibody reactive with a polypeptide of the invention or fragment thereof with a detectable label;
- b) administering the labeled antibody or labeled fragment to the patient; and
- c) detecting specifically bound labeled antibody or labeled fragment in the patient which indicates the presence of streptococcus.

A further aspect of the invention is the use of the GBS

polypeptides of the invention as immunogens for the production of specific antibodies for the diagnosis and in particular the treatment of streptococcus infection. Suitable antibodies may be determined using appropriate screening methods, for example by measuring the ability of a particular antibody to passively protect against streptococcus infection in a test model. One example of an animal model is the mouse model described in the examples herein. The antibody may be a whole antibody or an antigen-binding fragment thereof and may in general belong to any immunoglobulin class. The antibody or fragment may be of animal origin, specifically of mammalian origin and more specifically of murine, rat or human origin. It may be a natural antibody or a fragment thereof, or if desired, a recombinant antibody or antibody fragment. The term recombinant antibody or antibody fragment means antibody or antibody fragment which were produced using molecular biology techniques. The antibody or antibody fragments may be polyclonal, or preferably monoclonal. It may be specific for a number of epitopes associated with the GBS polypeptides but is preferably specific for one.

EXAMPLE 1 Murine model of lethal Group B Streptococcus (GBS) infection

The mouse model of GBS infection is described in detail in Lancefield et al (J Exp Med 142:165-179,1975). GBS strain C388/90 (Clinical isolate obtained in 1990 from the cephalorachidian fluid of a patient suffering from meningitis, Children's Hospital of Eastern Ontario, Ottawa, Canada) and NCS246 (National Center for Streptococcus, Provincial Laboratory of Public Health for Northern Alberta, Edmonton, Canada) were respectively serotyped as type Ia/c and type II/R.

To increase their virulence, the GBS strains C388/90 (serotype Ia/c) and NCS 246 (serotype II/R) were serially passaged through mice as described previously (Lancefield et al. J Exp Med 142:165-179, 1975). Briefly, the increase of virulence was monitored using intraperitoneal inoculations of serial dilutions of a subculture in Todd-Hewitt broth obtained from either the blood or spleen of infected mice. After the last passage, infected blood samples were used to inoculate Todd-Hewitt broth. After an incubation of 2 hours at 37°C with 7% CO<sub>2</sub>, glycerol at a final concentration of 10% (v/v) was added to the culture. The culture was then aliquoted and stored at -80° C for use in GBS challenge experiments. The number of cfu of GBS present in these frozen samples was determined. The bacterial concentration necessary to kill 100% (LD100) of the 18 weeks old mice were determined to be 3.5X10<sup>5</sup> and 1.1X10<sup>5</sup> respectively for GBS strain C388/90 and NCS246, which corresponded to a significant increase in virulence for both strains. Indeed, the LD100 recorded before the passages for these two strains was higher than 10<sup>9</sup> cfu.

In a bacterial challenge, a freshly thawed aliquot of a virulent GBS strain was adjusted to the appropriate bacterial concentration using Todd-Hewitt broth and 1ml was injected intraperitoneally to each female CD-1 mouse. The mice used for the passive protection experiments were 6 to 8 weeks old, while the ones used for the active protection experiments were approximately 18 weeks old at the time of the challenge. All inocula were verified by colony counts. Animals were observed for any sign of infection four times daily for the first 48 h after challenge and then daily for the next 12 days. At the end of that period, blood samples were obtained from the survivors and frozen at -20°C. The spleen obtained from each mouse that survived the challenge was cultured in order to identify any remaining GBS.

EXAMPLE 2 Immunization and protection in mice with formaldehyde killed whole GBS cells

- 5 Formaldehyde killed GBS whole cells were prepared according to the procedures described in Lancefield et al (J Exp Med 142:165-179,1975). Briefly, an overnight culture on sheep blood agar plates (Quelab Laboratories, Montreal, Canada) of a GBS strain was washed twice in PBS buffer (phosphate buffered-saline, pH7.2), adjusted to approximately  $3 \times 10^9$  cfu/mL and incubated overnight in PBS containing 0.3% (v/v) formaldehyde. The killed GBS suspension was washed with PBS and kept frozen at  $-80^{\circ}\text{C}$ .
- 15 Female CD-1 mice, 6 to 8 weeks old (Charles River, St-Constant, Québec, Canada), were injected subcutaneously three times at two weeks interval with 0.1 ml of formaldehyde killed cells of GBS strain C388/90 ( $\sim 6 \times 10^7$  GBS), or 0.1 ml of PBS for the control group. On the day before the immunization, Alhydrogel<sup>TM</sup> (Superfos Biosector, Frederikssund, Denmark) at a final concentration of 0.14 mg or 0.21 mg of Al, was added to these preparations and incubated overnight at  $4^{\circ}\text{C}$  with agitation. Serum samples were obtained from each mouse before the beginning of the immunization protocol and two weeks after the last injection. The sera were frozen at  $-20^{\circ}\text{C}$ .

- Eight mice in each control group injected with PBS and the group immunized with formaldehyde killed whole cells GBS strain C388/90 (Ia/c) were challenged with  $1.5 \times 10^4$  cfu of GBS strain C388/90 (Ia/c) one week after the third injection. All mice immunized with the formaldehyde killed GBS whole cells survived the homologous challenge while, within 5 days after the challenge, only 4 out of the 8 mice injected with PBS survived from the infection. In order to increase the mortality rate in the control groups, the

bacterial suspension had to be adjusted according to the age of the mice at the time of the bacterial challenge. In subsequent challenge experiments, when mice were older than 15 weeks, the bacterial inoculum was increased to

5 concentrations between  $3.0 \times 10^5$  and  $2.5 \times 10^6$  cfu.

Table 1 Immunization of CD1 mice with formaldehyde killed whole cells of GBS and subsequent homologous challenge [strain C388/90 (Ia/c)] and heterologous challenge [strain NCS246 (II/R)].

antigenic preparations used for immunization <sup>1</sup>	number of living mice 14 days after the bacterial challenge (% Survival)	
	homologous challenge: strain C388/90 (Ia/c)	heterologous challenge: strain NCS246 (II/R)
1st infection		
formaldehyde killed cells of GBS strain C388/90 (Ia/c) <sup>2</sup>	8/8 (100) <sup>3</sup>	n.d. <sup>5</sup>
control PBS	4/8 (50)	n.d.
2nd infection		
formaldehyde killed cells of GBS strain C388/90 (Ia/c)	6/6 (100) <sup>4</sup>	0/6 (0) <sup>6</sup>
control PBS	2/6 (33)	0/6 (0)

<sup>1</sup> alhydrogel™ at a final concentration of 0.14 mg or 0.21mg of Al was used;

<sup>2</sup> approximately  $6 \times 10^7$  cfu;

<sup>3</sup> intraperitoneal challenge with 1 mL Todd-Hewitt culture medium containing GBS C388/90 (Ia/c) suspension adjusted to  $1.5 \times 10^4$  cfu;

<sup>4</sup> intraperitoneal challenge with 1 mL Todd-Hewitt culture medium containing GBS C388/90 (Ia/c) suspension adjusted to  $2.1 \times 10^6$  cfu;

<sup>5</sup> not done;

<sup>6</sup> intraperitoneal challenge with 1 mL Todd-Hewitt culture medium containing GBS NCS246 (II/R) suspension adjusted to  $1.2 \times 10^5$  cfu.

In another experiment, one group of 12 mice corresponding to a control group was injected with PBS, while a second group of 12 mice was immunized with formaldehyde killed whole cells of GBS strain C388/90 (Ia/c). Six mice from each of these two groups were challenged with  $2.1 \times 10^6$  cfu of the GBS strain C388/90 (Ia/c) (Table I). As the first challenge experiment, all mice immunized with the GBS strain C388/90 (Ia/c) survived the homologous challenge. Only two out of the 6 mice injected with PBS survived the infection.

The remaining 6 mice in both groups were then used one week later to verify whether this antigenic preparation could confer cross protection against strain NCS246 (II/R) which produce a serologically distinct capsule. None of the mice infected with this second GBS strain survived the infection. The later result suggested that most of the protective immune response induced by formaldehyde killed strain C388/90 is directed against the capsular polysaccharide and that it could be restricted to strains of that particular serotype. These results clearly indicated that this particular model of infection can be efficiently used to study the protection conferred by vaccination.

15  
EXAMPLE 3 Immunization of rabbit with formaldehyde killed whole GBS cells and passive protection in mice

A New Zealand rabbit (2.5 kg, Charles River, St-Constant, Québec, Canada) was immunized with formaldehyde killed cells of GBS strain C388/90 (Ia/c) to obtain hyperimmune serum. This rabbit was injected subcutaneously three times at three weeks interval with approximately  $1.5 \times 10^9$  cfu of formaldehyde killed whole cells of GBS strain C388/90 (Ia/c). Freund's complete adjuvant (Gibco BRL Life Technologies, Grand Island, New York) was used as the adjuvant for the first immunization, while Freund's incomplete adjuvant (Gibco BRL) was used for the following two injections. Serum samples were obtained before the beginning of the immunization protocol and two weeks after the last injection. The sera were frozen at  $-20^{\circ}\text{C}$ .

The ability of this particular rabbit hyperimmune serum to passively protect mice against a lethal infection with GBS



was also evaluated. Intraperitoneal injection of mice with either 15 or 25  $\mu$ L of hyperimmune rabbit serum 18 hours before the challenge protected 4 out of 5 mice (80%) against the infection. Comparatively, survival rates lower than 20% were recorded for mice in the control group injected with PBS or serum obtained from a rabbit immunized with meningococcal outer membrane preparation. This result clearly indicates that the immunization of another animal species with killed GBS cells can induce the production of antibodies that can passively protect mice. This reagent will also be used to characterize clones.

Table 2 Passive protection of CD-1 mice conferred by rabbit serum obtained after immunization with formaldehyde killed group B whole streptococci (strain C388/90 (Ia/c)) antigenic preparation

groups	number of living mice 14 days after the bacterial challenge with GBS strain C388/90 (Ia/c) <sup>2</sup>	% survival
rabbit hyperimmune serum <sup>2</sup> - 25 $\mu$ l	4/5	80
rabbit hyperimmune serum <sup>1</sup> - 15 $\mu$ l	4/5	80
control rabbit serum - 25 $\mu$ l	1/5	20
control PBS	1/10	10

- <sup>1</sup> Freund's complete adjuvant was used for first immunization, and Freund's incomplete adjuvant for the following two injections;
- <sup>2</sup> intraperitoneal challenge with 1 ml Todd-Hewitt culture medium containing GBS C388/90 (Ia/c) suspension adjusted to  $2 \times 10^4$  cfu.

EXAMPLE 4 Recombinant production of His.Tag-GBS fusion protein

The coding region of a GBS gene was amplified by PCR (DNA Thermal Cyclor GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from the genomic DNA of GBS strain C388/90 (Ia/c) using the oligos that contained base extensions for the addition of the restriction sites BglIII (AGATCT) and HindIII (AAGCTT), respectively. The PCR product was purified from agarose gel using a Qiaex II gel extraction kit from Qiagen (Chatsworth, CA), digested with the restriction enzymes BglIII and HindIII (Pharmacia Canada Inc Baie d'Urfe, Canada), and extracted with phenol:chloroform before ethanol precipitation. The pET-32b(+) vector (Novagen, Madison, WI) containing the thioredoxin-His.Tag sequence was digested with the restriction enzymes BglIII and HindIII, extracted with phenol:chloroform, and then ethanol precipitated. The BglIII-HindIII genomic DNA fragment was ligated to the BglIII-HindIII pET-32b(+) vector to create the coding sequence for thioredoxin-His.Tag-GBS fusion protein whose gene was under control of the T7 promoter. The ligated products were transformed into *E. coli* strain XLI Blue MRF' ( $\Delta(mcrA)183\Delta(mcrCB-hsdSMR-mrr)173\ endA1\ supE44\ thi-1\ recA1\ gyrA96\ relA1\ lac\ [F'proAB\ lacI^qZAM15Tn10\ (Tet^r)]^c$ ) (Stratagene, La Jolla, CA) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed.), pp. 109-135). The recombinant pET plasmid was purified using a Qiagen kit (Qiagen, Chatsworth, CA) and the nucleotide sequence of the DNA insert was verified by DNA sequencing (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA). The recombinant pET plasmid was transformed by electroporation (Gene Pulser II apparatus, BIO-RAD Labs, Mississauga, Canada) into *E. coli* strain AD494 (DE3) ( $\Delta ara^+ leu7697\ \Delta lacX74\ \Delta phoA\ PvuII\ phoR\ \Delta malF3\ F'[lac^+(lacI^q)\ pro]\ trxB::Kan$  (DE3)) (Novagen, Madison, WI). In this strain of

*E. coli*, the T7 promoter controlling expression of the fusion protein, is specifically recognized by the T7 RNA polymerase (present on the  $\lambda$ DE3 prophage) whose gene is under the control of the lac promoter which is inducible by isopropyl- $\beta$ -D-thio-galactopyranoside (IPTG).

The transformant AD494(DE3)/rpET was grown at 37°C with agitation at 250 rpm in LB broth (peptone 10g/L, Yeast extract 5g/L, NaCl 10g/L) containing 100 $\mu$ g of ampicillin (Sigma-Aldrich Canada Ltd., Oakville, Canada) per mL until the  $A_{600}$  reached a value of 0.6. In order to induce the production of the thioredoxin-His.Tag-GBS fusion protein, the cells were incubated for 2 additional hours in the presence of IPTG at a final concentration of 1mM. The bacterial cells were harvested by centrifugation.

The recombinant fusion protein produced by AD494(DE3)/rpET32 upon IPTG induction for 2h was partially obtained as insoluble inclusion bodies which were purified from endogenous *E. coli* proteins by the isolation of insoluble aggregates (Gerlach, G.F. et al 1992, Infect. Immun. 60:892). Induced cells from a 500 mL culture were resuspended in 20 mL of 25% sucrose-50mM Tris-HCl buffer (pH8.0) and frozen at -70°C. Lysis of cells in thawed suspension was achieved by the addition of 5mL of a solution of lysozyme (10mg/mL) in 250mM Tris-HCl buffer (pH8.0) followed by an incubation of 10 to 15 min on ice, and the addition of 150mL of detergent mix (5 parts of 20mM Tris-HCl buffer [pH7.4]-300mM NaCl-2% deoxycholic acid-2% Nonidet P-40 and 4 parts of 100mM Tris-HCl buffer [pH8]-50mM EDTA-2% Triton X-100) followed by 5 min incubation on ice. Upon sonication, protein aggregates were harvested by centrifugation for 30 min at 35,000 X g and a sample of the soluble cellular fraction was kept. The aggregated proteins were solubilized in 6M guanidine hydrochloride. The

presence of the fusion protein in both the soluble and insoluble fractions was shown by Western Blot analysis using the serum of a mouse injected with formaldehyde killed cells of GBS strain C388/90 (Ia/c) that survived a bacterial  
5 challenge with the corresponding GBS strain.

The purification of the fusion protein from the soluble fraction of IPTG-induced AD494(DE3)/rpET was done by affinity chromatography based on the properties of the  
10 His.Tag sequence (6 consecutive histidine residues) to bind to divalent cations ( $\text{Ni}^{2+}$ ) immobilized on the His.Bind metal chelation resin (Novagen, Madison, WI). The purification method used are those described in the pET system Manual, 6th Edition (Novagen, Madison, WI). Briefly, the pelleted  
15 cells obtained from a 100mL culture induced with IPTG was resuspended in 4mL of Binding buffer (5mM imidazole-500mM NaCl-20mM Tris-HCl pH7.9), sonicated, and spun at 39,000 X g for 20 min to remove debris. The supernatant was filtered (0.45 $\mu$ m pore size membrane) and deposited on a column of  
20 His.Bind resin equilibrated in Binding buffer. The column was then washed with 10 column volumes of Binding buffer followed by 6 column volumes of Wash buffer (20mM imidazole-500mM NaCl-20mM Tris-HCl pH7.9). The thioredoxin-His.Tag-GBS fusion protein was eluted with Elute buffer (1M  
25 imidazole-500mM NaCl-20mM Tris-HCl pH7.9). The removal of the salt and imidazole from the sample was done by dialysis against 3 X 1 liter PBS at 4°C.

The quantities of fusion protein obtained from either the  
30 soluble or insoluble cytoplasmic fractions of *E. coli* were estimated by Coomassie staining of a sodium dodecyl sulfate (SDS)-polyacrylamide gel with serial dilutions of these proteins and a bovine serum albumin standard (Pierce Chemical Co. Rockford, Ill.).

35

EXAMPLE 5            Recombinant production of GBS protein under  
                         control of lambda P<sub>L</sub> promoter

The DNA coding region of a GBS protein was inserted  
5 downstream of the promoter  $\lambda P_L$  into the translation vector  
pURV22. This plasmid was derived from p629 (George et al,  
1987, Bio/Technology 5:600) from which the coding region for  
a portion of the herpes simplex virus type I (HSV-I)  
glycoprotein (gD-1) was removed and the ampicillin  
10 resistance gene replaced by a kanamycin cassette obtained  
from the plasmid vector pUC4K (Pharmacia Biotech Canada  
Inc., Baie D'Urfe, Canada). The vector contained a cassette  
of the bacteriophage  $\lambda$  cI857 temperature sensitive repressor  
gene from which the functional P<sub>R</sub> promoter had been deleted.  
15 The inactivation of the cI857 repressor by temperature  
increase from the ranges of 30-37°C to 37-42°C resulted in  
the induction of the gene under the control of  $\lambda P_L$ . The  
translation of the gene was controlled by the ribosome  
binding site cro followed downstream by a BglIII restriction  
20 site (AGATCT) and the ATG: ACTAAGGAGGTTAGATCTATG.

Restriction enzymes and T4 DNA ligase were used according to  
suppliers (Pharmacia Biotech Canada Inc., Baie D'Urfe,  
Canada; and New England Biolabs Ltd., Mississauga, Canada).  
25 Agarose gel electrophoresis of DNA fragments was performed  
as described by Sambrook et al. ( Molecular cloning : A  
laboratory Manual, 1989, Cold Spring Harbor Laboratory  
Press, N.Y). Chromosomal DNA of the GBS bacteria was  
prepared according to procedures described in Jayarao et al  
30 (J. Clin. Microbiol., 1991, 29:2774). DNA amplification  
reactions by polymerase chain reaction (PCR) were made using  
DNA Thermal Cycler GeneAmp PCR system 2400 (Perkin Elmer,  
San Jose, CA). Plasmids used for DNA sequencing were  
purified using plasmid kits from Qiagen (Chatsworth, CA).  
35 DNA fragments were purified from agarose gels using Qiaex II

gel extraction kits from Qiagen (Chatsworth, CA). Plasmid transformations were carried out by the method described by Hanahan (DNA Cloning, Glover (ed.) pp, 109-135, 1985). The sequencing of genomic DNA inserts in plasmids was done using  
5 synthetic oligonucleotides which were synthesized by oligonucleotide synthesizer model 394 (the Perkin-Elmer Corp., Applied Biosystems Div. (ABI), Foster City, CA). The sequencing reactions were carried out by PCR using the Taq Dye Deoxy Terminator Cycle Sequencing kit (ABI, Foster City,  
10 CA) and DNA electrophoresis was performed on automated DNA sequencer 373A (ABI, Foster City, CA). The assembly of the DNA sequence was performed using the program Sequencer 3.0 (Gene Codes Corporation, Ann Arbor, MI). Analysis of the DNA sequences and their predicted polypeptides was performed  
15 with the program Gene Works version 2.45 (Intelligenetics, Inc., Mountain View CA).

The coding region of the GBS gene was amplified by PCR from GBS strain C388/90 (Ia/c) genomic DNA using oligos that  
20 contained base extensions for the addition of restriction sites BglII (AGATCT) and XbaI (TCTAGA), respectively. The PCR product was purified from agarose gel using a Qiaex II gel extraction kit from Qiagen (Chatsworth, CA), digested with the restriction enzymes BglII and XbaI, and extracted with  
25 phenol:chloroform before ethanol precipitation. The pURV22 vector was digested with the restriction enzymes BglII and XbaI, extracted with phenol:chloroform, and ethanol precipitated. The BglII-XbaI genomic DNA fragment was ligated to the BglII-XbaI pURV22 vector in which the GBS  
30 gene was under the control of the  $\lambda$ PL promoter. The ligated products were transformed into *E. coli* strain XLI Blue MRF' ( $\Delta$  (mcrA)183 $\Delta$ (mcrCB-hsdSMR-mrr)173 endA1 supE44 thi-1 recA1 gyrA96 relA1 lac[F' proAB lacI<sup>q</sup>ZAM15 Tn10(Tet<sup>r</sup>)]<sup>c</sup>) (Stratagene, La Jolla CA) according to the methods described  
35 in Hanahan, supra. Transformants harboring plasmids with the

insert were identified by analysis of lysed cells submitted to electrophoresis on agarose gel (Sambrook et al, supra). The recombinant pURV22 plasmid was purified using a Qiagen kit (Qiagen, Chatsworth, CA) and the nucleotide sequence of the DNA insert was verified by DNA sequencing.

The transformant XLI Blue MRF'/rpURV22 was grown at 34°C with agitation at 250 rpm in LB broth containing 50µg of kanamycin per mL until the A<sub>600</sub> reached a value of 0.6. In order to induce the production of the fusion protein, the cells were incubated for 4 additional hours at 39°C. The bacterial cells were harvested by centrifugation, resuspended in sample buffer, boiled for 10 min and kept at -20°C.

#### EXAMPLE 6 Subcloning GBS protein gene in CMV plasmid pCMV-GH

The DNA coding region of a GBS protein was inserted in phase downstream of the human growth hormone (hGH) gene which was under the transcriptional control of the cytomegalovirus (CMV) promoter in the plasmid vector pCMV-GH (Tang et al, Nature, 1992, 356:152). The CMV promoter is non functional in E. coli cells but active upon administration of the plasmid in eukaryotic cells. The vector also incorporated the ampicillin resistance gene.

The coding region of the gene was amplified by PCR from genomic DNA of GBS strain C388/90 (Ia/c) using the oligos that contained base extensions for the addition of the restriction sites BglII (AGATCT) and HindIII (AAGCTT). The PCR product was purified from agarose gel using a Qiaex II gel extraction kit from Qiagen (Chatsworth, CA), digested with the restriction enzymes BglII and HindIII, and extracted with phenol:chloroform before ethanol precipitation. The pCMV-GH vector (Laboratory of Dr. Stephen

A. Johnston, Department of Biochemistry, The University of Texas, Dallas, Texas) containing the human growth hormone to create fusion proteins was digested with the restriction enzymes BamHI and HindIII, extracted with phenol:chloroform, and ethanol precipitated. The 1.3-kb BglIII-HindIII genomic DNA fragment was ligated to the BamHI -HindIII pCMV-GH vector to create the hGH-GBS fusion protein under the control of the CMV promoter. The ligated products were transformed into *E. coli* strain DH5 $\alpha$  [ $\phi$ 80 *lacZ*  $\Delta$ M15 *endA1* *recA1* *hsdR17* (<sup>r</sup>K<sup>-</sup>K<sup>+</sup>) *supE44* *thi-1* $\lambda^-$  *gyrA96* *relA1*  $\Delta$ (*lacZYA-argF*)U169] (Gibco BRL, Gaithersburg, MD) according to the methods described by Hanahan, supra. Transformants harboring plasmids with the insert were identified by analysis of lysed cells submitted to electrophoresis on agarose gel (Sambrook, J. et al, supra). The recombinant pCMV plasmid was purified using a Qiagen kit (Qiagen, Chatsworth, CA) and the nucleotide sequence of the DNA insert was verified by DNA sequencing.

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EXAMPLE 7 Immunological activity of GBS protein to GBS challenge

Four groups of 12 female CD-1 mice (Charles River, St-Constant, Quebec, Canada) of 6 to 8 weeks were injected subcutaneously three times at three week intervals with 0.1mL of the following antigenic preparations: formaldehyde killed cells of GBS strain C388/90 ( $\sim 6 \times 10^7$  cfu), 20 $\mu$ g of thioredoxin-His.Tag-GBS fusion protein obtained from the insoluble (inclusion bodies) or 20 $\mu$ g of the fusion protein, affinity purified (nickel column), from the soluble cytoplasmic fraction in *E. coli*, or 20 $\mu$ g of affinity purified (nickel column) thioredoxin-His.Tag control polypeptide. 20 $\mu$ g of QuilA<sup>TM</sup> (Cedarlane Laboratories Ltd, Hornby, Canada)



was added to each antigenic preparation as the adjuvant. Serum samples were obtained from each mouse before immunization (PB) and on days 20 (TB1), 41 (TB2) and 54 (TB3) during the immunization protocols. Sera were frozen at -20°C.

An increase of the ELISA titers was recorded after each injection of the fusion protein indicating a good primary response and a boost of the specific humoral immune response after each of the second and third administration. At the end of the immunization period, the means of reciprocal ELISA titers was 456,145 for the group immunized with 20µg of fusion protein obtained from inclusion bodies compared to 290,133 for the group of mice immunized with the protein from soluble fraction in *E.coli*. The latter result suggests that the protein obtained from inclusion bodies could be more immunogenic than the soluble protein. Analysis of mice sera in ELISA using the affinity purified thioredoxin-His.Tag to coat plates showed that negligible antibody titers are made against the thioredoxin-His.Tag portion of the fusion protein. The reactivity of the sera from mice injected with the recombinant fusion protein was also tested by ELISA against formaldehyde killed whole cells of GBS strain C388/90. The antibodies induced by immunization with recombinant fusion protein also recognized their specific epitopes on GBS cells indicating that their conformation is close enough to the native streptococcal protein to induce cross-reactive antibodies.

To verify whether the immune response induced by immunization could protect against GBS infection, mice were challenged with  $3.5 \times 10^5$  cfu of GBS strains C338/90(Ia/c) and  $1.2 \times 10^5$  cfu of strain NCS246(II/R) the results of which are illustrated in tables 3 and 4 respectively. Mice immunized with control thioredoxin-His.Tag peptide were not protected against challenge with either GBS strain while those

immunized with formaldehyde killed C388/90 whole cells only provided protection against homologous challenge. The thioredoxin-His.Tag-GBS fusion protein of the invention protected mice from challenge with both GBS strains. Blood  
5 and spleen culture of these mice did not reveal the presence of any GBS.

Table 3 Survival from GBS strain C388/90 (Ia/c) challenge<sup>1</sup>

immunizing agent	no. mice surviving challenge	% survival
thioredoxin-His.Tag <sup>2</sup>	1 / 6	17
formaldehyde killed C388/90 cells <sup>3</sup>	6 / 6	100
thioredoxin-His.Tag-GBS fusion (inclusion body preparation) <sup>4</sup>	6 / 6	100
thioredoxin-His.Tag-GBS fusion (cytoplasmic fraction) <sup>4</sup>	6 / 6	100

- 5 <sup>1</sup> intraperitoneal administration with 1 ml Todd-Hewitt culture medium adjusted to  $3.5 \times 10^5$  cfu;
- <sup>2</sup> 20µg administered; posterior legs paralyzed in surviving mouse; GBS detected in blood and spleen;
- <sup>3</sup>  $6 \times 10^7$  cfu administered;
- <sup>4</sup> 20µg administered.

Table 4 Survival from GBS strain NCS246 (II/R) challenge<sup>1</sup>

immunizing agent	no. mice surviving challenge	% survival
thioredoxin-His.Tag <sup>2</sup>	0 / 6	0
formaldehyde killed C388/90 cells <sup>3</sup>	2 / 6	34
thioredoxin-His.Tag-GBS fusion (inclusion body preparation) <sup>2</sup>	5 / 5 <sup>4</sup>	100
thioredoxin-His.Tag-GBS fusion (cytoplasmic fraction) <sup>2</sup>	6 / 6	100

5   <sup>1</sup> intraperitoneal administration with 1 ml Todd-Hewitt  
culture medium containing GBS NCS246 (II/R) suspension  
adjusted to  $1.2 \times 10^5$  cfu.

<sup>2</sup> 20 µg administered;

<sup>3</sup>  $6 \times 10^7$  cfu administered;

10   <sup>4</sup> one mouse died during immunization.

#### EXAMPLE 8 Immunization with recombinant GBS protein confers protection against experimental GBS infection

15

This example illustrates the protection of mice against  
fatal GBS infection by immunization with the recombinant  
protein corresponding to the SEQ ID NO:39.

20 Groups of 10 female CD-1 mice (Charles River) were immunized  
subcutaneously three times at three-week intervals with 20  
µg of recombinant protein purified from E. coli strain BLR  
(Novagen) harboring the recombinant pURV22 plasmid vector  
containing the GBS gene corresponding to SEQ ID NO:42 in  
25 presence of 20 µg of QuilA<sup>TM</sup> adjuvant (Cedarlane  
Laboratories Ltd, Hornby, Canada) or, as control, with

QuilA™ adjuvant alone in PBS. Blood samples were collected from the orbital sinus on day 1, 22 and 43 prior to each immunization and fourteen days (day 57) following the third injection. One week later the mice were challenged with

5 approximately  $10^4$  to  $10^6$  CFU of various virulent GBS strains.

Samples of the GBS challenge inoculum were plated on TSA/5% sheep blood agar plates to determine the CFU and to verify the challenge dose. Deaths were recorded for a period of 14 days and on day 14 post-challenge, the surviving mice were  
10 sacrificed and blood and spleen were tested for the presence of GBS organisms. The survival data are shown in table 5.

Prechallenge sera were analyzed for the presence of antibodies reactive with GBS by standard immunoassays. Elisa  
15 and immunoblot analyses indicated that immunization with recombinant GBS protein produced in *E. coli* elicited antibodies reactive with both, recombinant and native GBS protein. Antibody responses to GBS are described in Example  
9.

20

Table 5. Ability of recombinant GBS protein corresponding to SEQ ID NO: 39 to elicit protection against 8 diverse GBS challenge strains

Immunogen	Challenge strain		No. alive: No. dead <sup>1</sup>	
	Designation	Type		
rGBS protein none	C388/90	Ia/c	8 : 2 0 : 10	(P<0.0001)
rGBS protein none	NCS 246	II/R	10 : 0 3 : 7	(P=0.0012)
rGBS protein none	ATCC12401	Ib	10 : 0 3 : 7	(P=0.001)
rGBS protein none	NCS 535	V	10 : 0 5 : 5	(P=0.01)
rGBS protein none	NCS 9842	VI	10 : 0 0 : 10	(P<0.0001)
rGBS protein NCS 915-F <sup>3</sup> none	NCS 915	III	7 : 3 1 : 9 4 : 6	(P=0.0007) <sup>2</sup>
rGBS protein NCS 954-F none	NCS 954	III/R	7 : 3 4 : 6 1 : 9	( P=0.002)
rGBS protein COH1-F none	COH1	III	4 : 6 3 : 7 0 : 10	(P=0.0004)

<sup>1</sup> Groups of 10 mice per group were used, the number of mice surviving to infection and the number of dead mice are indicated. The survival curves corresponding to recombinant GBS protein-immunized animals were compared to the survival curves corresponding to mock-immunized animals using the log-rank test for nonparametric analysis.

<sup>2</sup> Comparison analysis to NCS915-F-immunized animals.

<sup>3</sup> Animals were immunized with formaldehyde-killed GBS in presence of QuilA<sup>TM</sup> adjuvant.

All hemocultures from surviving mice were negative at day 14 post-challenge. Spleen cultures from surviving mice were negative except for few mice from experiment MB-11.

EXAMPLE 9 Vaccination with the recombinant GBS protein  
elicits an immune response to GBS

5 Groups of 10 female CD-1 mice were immunized subcutaneously  
with recombinant GBS protein corresponding to SEQ ID NO:39  
as described in Example 8. In order to assess the antibody  
response to native GBS protein, sera from blood samples  
collected prior each immunization and fourteen days after  
the third immunization were tested for antibody reactive  
10 with GBS cells by ELISA using plates coated with  
formaldehyde-killed GBS cells from type III strain NCS 954,  
type Ib strain ATCC12401, type V strain NCS 535 or type VI  
strain NCS 9842. The specificity of the raised antibodies  
for GBS protein was confirmed by Western blot analyses to  
15 GBS cell extracts and purified recombinant antigens. The  
results shown in Figure 10 clearly demonstrate that animals  
respond strongly to recombinant GBS protein used as  
immunogens with median reciprocal antibody titers varying  
between 12000 and 128000, for sera collected after the third  
20 immunization, depending of the coating antigen. All  
preimmune sera were negative when tested at a dilution of  
1 :100. GBS-reactive antibodies were detectable in the sera  
of each animal after a single injection of recombinant GBS  
protein.

25

Example 10 Antigenic conservation of the GBS protein of the present invention

5 Monoclonal antibodies (MAbs) specific to the GBS protein of the present invention were used to demonstrate that this surface antigen is produced by all GBS and that it is also antigenically highly conserved.

10 A collection of 68 GBS isolates was used to evaluate the reactivity of the GBS-specific MAbs. These strains were obtained from the National Center for Streptococcus, Provincial Laboratory of Public Health for Northern Alberta, Canada; Centre Hospitalier Universitaire de Quebec, Pavillon CHUL, Quebec, Canada; American Type Culture Collection, USA; 15 Laboratoire de Sante Publique du Quebec, Canada; and Dept. of Infectious Disease, Children's Hospital and Medical Center, Seattle, USA. All eight Mabs were tested against the following panel of strains: 6 isolates of serotype Ia or Ia/c, 3 isolates of serotype Ib, 4 isolates of serotype II, 20 14 isolates of serotype III, 2 isolates of serotype IV, 2 isolates of serotype V, 2 isolates of serotype VI, 2 isolates of serotype VII, 1 isolate of serotype VIII, 10 isolates that were not serotyped and 3 bovine *S. agalactiae* strains. MAb 3A2 was also reacted with additional GBS: 9 25 isolates of serotype Ia/c and 10 isolates of serotype V. The strains were grown overnight on blood agar plates at 37°C in an atmosphere of 5% CO<sub>2</sub>. Cultures were stored at - 70°C in heart infusion broth with 20% (v/v) glycerol.

30 To obtain the GBS protein-specific MAbs, mice were immunized three times at three-week intervals with 20 µg of purified recombinant GBS protein (SEQ ID NO :44) in the presence of 20% QuilA™ adjuvant. Hybridoma cell lines were generated by fusion of spleen cells recovered from immunized mice with 35 the nonsecreting SP2/O myeloma cell line as described



previously (Hamel, J. et al. 1987. J. Med. Microbiol. 23:163-170). Hybrid clone supernatants were tested for specific antibody production by ELISA using formaldehyde inactivated GBS and purified recombinant GBS protein (SEQ ID NO :39 or 44) as coating antigen, as previously described (Hamel, J. et al. 1987. J. Med. Microbiol. 23:163-170). Specific hybrid were cloned by limiting dilutions, expanded, and frozen in liquid nitrogen. Production of recombinant GBS protein was presented in Examples 4 & 5. Purified recombinant GBS protein or formaldehyde inactivated GBS were resolved by electrophoresis by using the discontinuous buffer system of Laemmli as recommended by the manufacturer and then transfer onto nitrocellulose membrane for Western immunoblotting as described previously (Martin et al. 1992. Infect. Immun. 60:2718-2725).

Western immunoblotting experiments clearly indicated that all eight MAbs recognized a protein band that corresponded to the purified recombinant GBS protein (SEQ ID NO :39). These MAbs also reacted with a protein band present in every GBS isolates tested so far. The reactivity of these GBS-specific MAbs are presented in Table 6. Each MAb reacted well with all 46 GBS. In addition, these MAbs also recognized the 3 *S. agalactiae* strains of bovine origin that were tested. MAb 3A2 also recognized nineteen GBS; 9 isolates of serotype Ia/c and 10 of serotype V. The other MAbs were not tested against these additional strains.

These results demonstrated that the GBS protein (SEQ ID NO :39) was produced by all the 65 GBS and the three *S. agalactiae* strains of bovine origin that were tested so far.

More importantly, these results clearly demonstrated that the epitopes recognized by these eight GBS-specific MAbs were widely distributed and conserved among GBS. These results also indicated that these epitopes were not

restricted to serologically related isolates since representatives of all known GBS serotypes including the major disease causing groups were tested.

- 5 In conclusion, the data presented in this example clearly demonstrated that the GBS protein of the present invention is produced by all GBS and that it is antigenically highly conserved.

10

Table 6. Reactivity of eight GBS protein-specific MAb with different *S. agalactiae* strains as evaluated by Western immunoblots.

Mabs	Number of each serotype of <i>s. agalactiae</i> strains recognized by the MAb <sub>s</sub> .											
	Ia or Ia/c (6)	Ib (3)	II (4)	III (4)	IV (2)	V (2)	VI (2)	VII (2)	VIII (1)	NT (10) 2	TOTAL (26)	Bovine (3)
3A21	6	3	4	4	2	2	2	2	1	10	46	3
5A12	6	3	4	4	2	2	2	2	1	10	46	3
6G11	6	3	4	4	2	2	2	2	1	10	46	2
8B9	6	3	4	4	2	2	2	2	1	10	46	3
8E11	6	3	4	4	2	2	2	2	1	10	46	3
12B12	6	3	4	4	2	2	2	2	1	10	46	3
18F11	6	3	4	4	2	2	2	2	1	10	46	3
20G2	6	3	4	4	2	2	2	2	1	10	46	3

<sup>1</sup> Nine additional strains of serotype Ia/c and 10 strains of serotype V were recognized by MAb 3A2.

<sup>2</sup> These strains were not serotyped

## WE CLAIM:

1. An isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide having a sequence selected from the group consisting of:  
SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5,  
SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10,  
SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15,  
SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19,  
SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24,  
SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29,  
SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34,  
SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39,  
SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or  
fragments, analogs or derivatives thereof.
2. A polynucleotide according to claim 1, wherein said polynucleotide encodes a polypeptide having at least 95% identity to the second polypeptide.
3. An isolated polynucleotide encoding a polypeptide capable of generating antibodies having binding specificity for a polypeptide having a sequence selected from the group consisting of:  
SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5,  
SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10,  
SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15,  
SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19,  
SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24,  
SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29,  
SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34,  
SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39,  
SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or  
fragments, analogs or derivatives thereof.

4. An isolated polynucleotide that is complementary to the polynucleotide of claim 1.
5. An isolated polynucleotide that is complementary to the polynucleotide of claim 3.
6. The polynucleotide of claim 1, wherein said polynucleotide is DNA.
7. The polynucleotide of claim 3, wherein said polynucleotide is DNA.
8. The polynucleotide of claim 1, wherein said polynucleotide is RNA.
9. The polynucleotide of claim 3, wherein said polynucleotide is RNA.
10. A polynucleotide which hybridizes under stringent conditions to a second polynucleotide having a sequence selected from the group consisting of :  
SEQ ID NO : 1, SEQ ID NO : 7, SEQ ID NO : 13, SEQ ID NO : 22, SEQ ID NO : 27, SEQ ID NO : 32, SEQ ID NO : 37, SEQ ID NO : 42 and SEQ ID NO : 43 or fragments, analogues or derivatives thereof.
11. A polynucleotide which hybridizes under stringent conditions to a second polynucleotide having a sequence selected from the group consisting of :  
SEQ ID NO : 37, SEQ ID NO : 42 and SEQ ID NO : 43.
12. A polynucleotide according to claim 11 which hybridizes under stringent conditions to a second polynucleotide having the sequence SEQ ID NO : 37.

13. A polynucleotide according to claim 11 which hybridizes under stringent conditions to a second polynucleotide having the sequence SEQ ID NO : 42.
14. A polynucleotide according to claim 11 which hybridizes under stringent conditions to a second polynucleotide having the sequence SEQ ID NO : 43.
15. A polynucleotide according to claim 10 wherein said polynucleotide has at least 95% complementarity to the second polynucleotide.
16. A polynucleotide according to claim 11 wherein said polynucleotide has at least 95% complementarity to the second polynucleotide.
17. A vector comprising the polynucleotide of claim 1, wherein said polynucleotide is operably linked to an expression control region.
18. A vector comprising the polynucleotide of claim 3, wherein said polynucleotide is operably linked to an expression control region.
19. A host cell transfected with the vector of claim 17.
20. A host cell transfected with the vector of claim 18.
21. A process for producing a polypeptide comprising culturing a host cell according to claim 19 under conditions suitable for expression of said polypeptide.
22. A process for producing a polypeptide comprising culturing a host cell according to claim 20 under condition suitable for expression of said polypeptide.

23. An isolated polypeptide having at least 70% identity to a second polypeptide having a sequence selected from the group consisting of:

SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

24. The isolated polypeptide of claim 23 having a sequence according to SEQ ID NO : 39.

25. The isolated polypeptide of claim 23 having a sequence according to SEQ ID NO : 44.

26. An isolated polypeptide capable of generating antibodies having binding specificity for a second polypeptide having a sequence selected from the group consisting of:

SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

27. The isolated polypeptide of claim 26 having a sequence according to SEQ ID NO : 39.
28. The isolated polypeptide of claim 26 having a sequence according to SEQ ID NO : 44.
29. An isolated polypeptide having an amino acid sequence selected from the group consisting of:  
SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5,  
SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10,  
SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15,  
SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19,  
SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24,  
SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29,  
SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34,  
SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39,  
SEQ ID NO:40 and SEQ ID NO:41 or fragments, analogs or derivatives thereof.
30. The isolated polypeptide of claim 29 having an amino acid sequence according to SEQ ID NO : 39.
31. An isolated polypeptide having an amino acid sequence according to SEQ ID NO : 44.
32. An isolated polypeptide according to any one of claims 29 to 31, wherein the N-terminal Met residue is deleted.
33. An isolated polypeptide according to any one of claims 29 to 30, wherein the secretory amino acid sequence is deleted.
34. A vaccine composition comprising a polypeptide according to any one of claims 23 to 31 and a pharmaceutically acceptable carrier, diluent or adjuvant.



35. A vaccine composition comprising a polypeptide according to claim 32 and a pharmaceutically acceptable carrier, diluent or adjuvant.
36. A vaccine composition comprising a polypeptide according to claim 33 and a pharmaceutically acceptable carrier, diluent or adjuvant.
37. A method for therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of a composition according to claim 34.
38. A method for therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of a composition according to claim 35.
39. A method for therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of a composition according to claim 36.
40. A method according to any one of claims 37 to 39, wherein said animal is a bovine.
41. A method according to any one of claims 37 to 39, wherein said animal is a human.

42. A method according to any one of claims 37 to 39, wherein said bacterial infection is selected from the group consisting of group A streptococcus and group B streptococcus.
43. A method according to claim 42, wherein said bacterial infection is group B streptococcus.
44. Use of a vaccine composition according to claim 34 for the therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to or infected with streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.
45. Use of a vaccine composition according to any one of claims 35 to 36 for the therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to or infected with streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.
46. Use of a vaccine composition according to any one claims 23 to 31 for the manufacture of a vaccine for the therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.
47. Use of a vaccine composition according to claim 32 for the manufacture of a vaccine for the therapeutic or

prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.

48. Use of a vaccine composition according to claim 33 for the manufacture of a vaccine for the therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.

TATCTGGCAA AGAGCCAGCT AATCGTTTTA GTTGGGCTAA AAATAAATTA TTAATCAATG 60  
 S G K E P A N R F S W A K N K L L I N G  
 ----->  
 GATTCATTGC AACTCTAGCA GCAACTATCT TATTTTTTGC AGTTCAATTC ATAGGTCTTA 120  
 F I A T L A A T I L F F A V Q F I G L K  
 AACCAGATTA CCCTGGAAAA ACCTACTTTA TTATCCTATT GACAGCATGG ACTTTGATGG 180  
 P D Y P G K T Y F I I L L T A W T L M A  
 CATTAGTAAC TGCTTTAGTG GGATGGGATA ATAGGTATGG TTCCTTCTTG TCGTTATTAA 240  
 L V T A L V G W D N R Y G S F L S L L I  
 TATTATTATT CCAGCTTGGT TCAAGCGCAG GAACTTACCC AATAGAATTG AGTCCTAAGT 300  
 L L F Q L G S S A G T Y P I E L S P K F  
 TCTTTCAAAC AATTCAACCA TTTTACCGA TGACTTACTC TGTTCAGGA TTAAGAGAGA 360  
 F Q T I Q P F L P M T Y S V S G L R E T  
 CCATCTCGTT GACGGGAGAC GTTAACCATC AATGGAGAAT GCTAGTAATC TTTTLAGTAT 420  
 I S L T G D V N H Q W R M L V I F L V S  
 CATCGATGAT ACTTGCTCTT CTTATTTATC GTAAACAAGA AGATTAATAG AAAGTATCTA 480  
 S M I L A L L I Y R K Q E D  
 GTGATAGACT AACAGTATGA TATGGTATGT CAAAGTATTT AGGAGGAGAA GATATGTCTA 540  
 M S T  
 |----->  
 CTTTAACAAT AATTATTGCA ACATTAACCTG CTTTGGAACA TTTTATATTT ATGTATTTGG 600  
 L T I I I A T L T A L E H F Y I M Y L E  
 AGACGTTAGC CACCCAGTCA AATATGACTG GGAAGATTTT TAGTATGTCT AAAGAAGAGT 660  
 T L A T Q S N M T G K I F S M S K E E L  
 TGTCAATTTT ACCCGTTATT AAACCTTTTTA AGAATCAAGG TGTATACAAC GGCTTGATTG 720  
 S Y L P V I K L F K N Q G V Y N G L I G  
 GCCTATTCCT CTTTATGCGG TTATATATTT CACAGAATCA AGAAATTGTA GCTGTTTTTT 780  
 L F L L Y G L Y I S Q N Q E I V A V F L  
 TAATCAATGT ATTGCTAGTT GCTATTTATG GTGCTTTGAC AGTTGATAAA AAAATCTTAT 840  
 I N V L L V A I Y G A L T V D K K I L L  
 TAAAACAGGG TGGTTTACCT ATATTAGCTC TTTTAACATT CTTATTTTAA TACTACTTAG 900  
 K Q G G L P I L A L L T F L F  
 CCGTTCGATT TAGTTGAACG GCTTTTAGTA ATCATTTTTT TCTCATAATA CAGGTAGTTT 960  
 AAGTAATTTG TCTTTAAAA TAGTATAATA TAACTACGAA TTCAAAGAGA GGTGACTTTG 1020  
 ATTATGACTG AGAACTGGTT ACATACTAAA GATGGTTCAG ATATTTATTA TCGTGTCGTT 1080  
 M T E N W L H T K D G S D I Y Y R V V  
 |----->  
 GGTCAAGGTC AACCGATTGT TTTTTTACAT GGCAATAGCT TAAGTAGTCG CTATTTTGAT 1140  
 G Q G Q P I V F L H G N S L S S R Y F D  
 AAGCAAATAG CATATTTTTC TAAGTATTAC CAAGTTATTG TTATGGATAG TAGAGGGCAT 1200  
 K Q I A Y F S K Y Y Q V I V M D S R G H  
 GGCAAAAGTC ATGCAAAGCT AAATACCATT AGTTTCAGGC AAATAGCAGT TGACTTAAAG 1260  
 G K S H A K L N T I S F R Q I A V D L K

GATATCTTAG TTCATTTAGA GATTGATAAA GTTATATTGG TAGGCCATAG CGATGGTGCC 1320  
 D I L V H L E I D K V I L V G H S D G A  
 AATTTAGCTT TAGTTTTTCA AACGATGTTT CCAGGTATGG TTAGAGGGCT TTTGCTTAAT 1380  
 N L A L V F Q T M F P G M V R G L L L N  
 TCAGGGAACC TGACTATTCA TGGTCAGCGA TGGTGGGATA TTCTTTTAGT AAGGATTGCC 1440  
 S G N L T I H G Q R W W D I L L V R I A  
 TATAAATTCC TTCACTATTT AGGGAAACTC TTTCCGTATA TGAGGCAAAA AGCTCAAGTT 1500  
 Y K F L H Y L G K L F P Y M R Q K A Q V  
 ATTTGCTTA TGTTGGAGGA TTTGAAGATT AGTCCAGCTG ATTTACAGCA TGTGTCAACT 1560  
 I S L M L E D L K I S P A D L Q H V S T  
 CCTGTAATGG TTTTGGTTGG AAATAAGGAC ATAATTAAGT TAAATCATTC TAAGAAACTT 1620  
 P V M V L V G N K D I I K L N H S K K L  
 GCTTCTTATT TTCCAAGGGG GGAGTTTTAT TCTTTAGTTG GCTTTGGGCA TCACATTATT 1680  
 A S Y F P R G E F Y S L V G F G H H I I  
 AAGCAAGATT CCCATGTTTT TAATATTATT GCAAAAAAGT TTATCAACGA TACGTTGAAA 1740  
 K Q D S H V F N I I A K K F I N D T L K  
 GGAGAAATTG TTGAAAAAGC TAATTGAAAA AGTCAAATCA CTGACTTCTG TGATTAAAT 1800  
 G E I V E K A N  
 TGTATTTTTT ATATCTGTTT TAGTGCTTAT TATTGTTGAA ATGATTCATT TGAAACGAAC 1860  
 M I H L K R T  
 |---->  
 TATTTCTGTT GAGCAACTAA AGAGTGTTTT TGGGCAATTA TCTCCAATGA ATCTTTTCTT 1920  
 I S V E Q L K S V F G Q L S P M N L F L  
 AATTATCCTT GTGGGGGTTA TCGCTGTCTT ACCGACAACC GGATATGACT TTGTACTGAA 1980  
 I I L V G V I A V L P T T G Y D F V L N  
 TGGACTTTTA CGTACAGATA AAAGCAAAAG GTATATTTTA CAGACTAGTT GGTGTATCAA 2040  
 G L L R T D K S K R Y I L Q T S W C I N  
 CACTTTAAT AACTTGTCAG GATTCGGTGG CTTAATCGAT ATTGGGTTGC GCATGGCTTT 2100  
 T F N N L S G F G G L I D I G L R M A F  
 TTATGGTAAA AAAGGTCAAG AGAAGAGTGA CCTAAGAGAA GTGACTCGTT TTTTACCCTA 2160  
 Y G K K G Q E K S D L R E V T R F L P Y  
 TCTATTTCT GGTCTGTCAT TTATTAGTGT GATTGCCTTA ATCATGAGCC ATATTTTCA 2220  
 L I S G L S F I S V I A L I M S H I F H  
 TGCCAAAGCT AGTGTGATT ACTATTATTT GGTATTAATT GGTGCTAGTA TGTATTTTCC 2280  
 A K A S V D Y Y Y L V L I G A S M Y F P  
 TGTTATTTAT TGGATTTCTG GTCATAAAGG AAGCCATTAT TTCGGAGATA TGCCATCTAG 2340  
 V I Y W I S G H K G S H Y F G D M P S S  
 TACTCGTATA AAATTAGGTG TTGTTTCTTT TTTTGAATGG GGATGTGCGG CCGCAGCATT 2400  
 T R I K L G V V S F F E W G C A A A A F  
 TATAATTATC GGTATTTTAA TGGGCATTCA TCTACCAGTT TATAAAATTT TACCACTATT 2460  
 I I I G Y L M G I H L P V Y K I L P L F

TTGTATTGGT TGTGCCGTCG GGATTGTATC CCTTATTCCC GGTGGATTAG GAAGTTTTGA 2520  
 C I G C A V G I V S L I P G G L G S F E  
 ATTAGTTCTA TTTACAGGGT TTGCTGCCGA GGGACTACCT AAAGAAACTG TGGTTGCATG 2580  
 L V L F T G F A A E G L P K E T V V A W  
 GTTATTACTT TATCGTTTAG CCTACTATAT TATTCCATTG TTTGCAGGTA TCTATTTCTT 2640  
 L L L Y R L A Y Y I I P F F A G I Y F F  
 TATCCATTAT TTAGGTAGTC AAATAAATCA ACGTTATGAA AATGTCCCGA AAGAGTTAGT 2700  
 I H Y L G S Q I N Q R Y E N V P K E L V  
 ATCAACTGTT CTACAAACCA TGGTGAGCCA TTTGATGCGT ATTTTAGGTG CATTCTTAAT 2760  
 S T V L Q T M V S H L M R I L G A F L I  
 |---->  
 ATTTTCAACA GCATTTTTTG AAAATATTAC TTATATTATG TGGTTGCAGA AGCTAGGCTT 2820  
 F S T A F F E N I T Y I M W L Q K L G L  
 GGACCCATTA CAAGAACAAA TGTTATGGCA GTTTCAGGT TTATTGCTGG GGGTTTGT 2880  
 D P L Q E Q M L W Q F P G L L L G V C F  
 TATTCTCTTA GCTAGAACTA TTGATCAAAA AGTGAAAAAT GCTTTTCCAA TTGCTATTAT 2940  
 I L L A R T I D Q K V K N A F P I A I I  
 CTGGATTACT TTGACATTGT TTTATCTTAA TTTAGGTCAT ATTAGTTGGC GACTATCTTT 3000  
 W I T L T L F Y L N L G H I S W R L S F  
 CTGGTTTATT TTAATTATTG TAGGCTTATT AGTCATTAAG CCAACTCTCT ATAAAAACA 3060  
 W F I L L L L G L L V I K P T L Y K K Q  
 ATTTATTTAT AGCTGGGAAG AGCGTATTAA GGATGGAATC ATTATCGTTA GTTTAATGGG 3120  
 F I Y S W E E R I K D G I I I V S L M G  
 AGTTCTATTT TATATTGCAG GACTACTATT CCCTATCAGG GCTCATATTA CAGGTGGTAG 3180  
 V L F Y I A G L L F P I R A H I T G G S  
 TATTGAACGC CTGCATTATA TCATAGCATG GGAGCCGATA GCATTGGCTA CGTTGATTCT 3240  
 I E R L H Y I I A W E P I A L A T L I L  
 TACTCTCGTT TATTTATGTT TGGTTAAGAT TTTACAAGGA AAATCTTGTC AGATTGGTGA 3300  
 T L V Y L C L V K I L Q G K S C Q I G D  
 TGTGTTCAAT GTGGATCGTT ATAAAAAACT ACTTCAAGCT TACGGTGGTT CTTCGGATAG 3360  
 V F N V D R Y K K L L Q A Y G G S S D S  
 CGGTTTAGCC TTTTAAATG ATAAAAGGCT CTAAGGTAC CAAAAAATG GAGAAGATTG 3420  
 G L A F L N D K R L Y W Y Q K N G E D C  
 CGTTGCGTTC CAATTTGTAA TTGTCAATAA TAAATGTCTT ATTATGGGGG AACCAGCCGG 3480  
 V A F Q F V I V N N K C L I M G E P A G  
 TGATGACACT TATATTCGTG AAGCTATTGA ATCGTTTATT GATGATGCTG ATAAGCTAGA 3540  
 D D T Y I R E A I E S F I D D A D K L D  
 CTATGACCTT GTTTTTTACA GTATTGGACA GAAGTTGACA CTACTTTTAC ATGAGTATGG 3600  
 Y D L V F Y S I G Q K L T L L L H E Y G  
 TTTTGACTTT ATGAAAGTTG GTGAGGATGC TTTAGTTAAT TTAGAAACGT TTAATCTTAA 3660  
 F D F M K V G E D A L V N L E T F T L K

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AGGGAATAAG TACAAACCTT TCAGAAATGC CCTAAATAGA GTTGAAAAGG ATGGTTTCTA 3720
G N K Y K P F R N A L N R V E K D G F Y

TTTCGAAGTT GTACAATCGC CACATAGTCA AGAGCTACTA AATAGTTTGG AAGAGATTTTC 3780
F E V V Q S P H S Q E L L N S L E E I S

TAATACTTGG TTAGAAGGAC GTCCTGAAAA AGGTTTCTCA CTAGGATATT TTAATAAAGA 3840
N T W L E G R P E K G F S L G Y F N K D

TTATTTCCAA CAAGCCCCAA TAGCTTTGGT AAAAAATGCT GAACACGAAG TTGTTGCTTT 3900
Y F Q Q A P I A L V K N A E H E V V A F

TGCTAATATT ATGCCAAACT ATGAAAAGAG TATTATCTCT ATTGATTTAA TGCCTCACGA 3960
A N I M P N Y E K S I I S I D L M R H D

TAAACAGAAA ATTCCGAATG GCGTTATGGA TTTCCTCTTT TTATCATTAT TCTCTTATTA 4020
K Q K I P N G V M D F L F L S L F S Y Y

TCAAGAGAAG GGATACCACT ATTTTGATTT GGGGATGGCA CCTTTATCAG GAGTTGGTCG 4080
Q E K G Y H Y F D L G M A P L S G V G R

CGTTGAAACA AGTTTGTCTA AAGAGAGAAT GCGGTATCTT GTCTATCATT TCGGTAGTCA 4140
V E T S F A K E R M A Y L V Y H F G S H

TTTCTACTCA TTTAATGGTT TACACAAGTA TAAGAAGAAG TTTACACCAT TGTGGTCGGA 4200
F Y S F N G L H K Y K K K F T P L W S E

ACGTTATATT TCTTGTCTC GTTCGTCCTG GTTAATTTGT GCTATTTGTG CCCTATTAAT 4260
R Y I S C S R S S W L I C A I C A L L M

GGAAGATAGT AAAATTAAGA TTGTTAAATA AGCTTTATTT GGCAATTAAA AAGAGCATGT 4320
E D S K I K I V K

CATGCGACAT GCTCTTTTAA AATCATTTAA TACCATTGAT TGCTTGAATC TACTTTATAA 4380

TATGATGTGC TTTTAAATAT TGTTTAGCTA CTGTAGCTGC TGATTTATGC TTTACAGCTA 4440

CTTGGTAGTT CATTTCTTGC ATTTCTTTTT CAGTGATATG ACCAGCAAGT TTATTGAGAG 4500

CTTTTTTTTAC TTGA (SEQ ID NO:1) 4514

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FIG. 1a  
[clone1-dna/aa]

SGKEPANRFS WAKNKLLING FIATLAATIL FFAVQFIGLK PDYPGKTYFI 50  
ILLTAWTLMA LVTALVGWDN RYGSFLLSLI LLFQLGSSAG TYPIELSPKF 100  
FQTIQPFLLPM TYSVSGLRET ISLTGDVNHQ WRMLVIFLVS SMILALLIYR 150  
KQED (SEQ ID NO:2) 154

FIG. 1b

MSTLTIIIIAT LTALEHFIYIM YLETLATQSN MTGKIFSMSK EELSYLPVIK 50  
LFKNQGVYNG LIGLFLLYGL YISQNQEIVA VFLINVLLVA IYGALTVDKK 100  
ILLKQGGLPI LALLTFLF (SEQ ID NO:3) 118

FIG. 1c

MTENWLHTKD GSDIYYRVVG QGQPIVFLHG NSLSSRYFDK QIAYFSKYYQ 50  
VIVMDSRGHG KSHAKLNTIS FRQIAVDLKD ILVHLEIDKV ILVGHSDGAN 100  
LALVFQTMFP GMVRGLLLS GNLTIHGQRW WDILLVRIAY KFLHYLGKLF 150  
PYMRQKAQVI SLMLDLKIS PADLQHVSTP VMVLVGKNKI IKLNHSHKLA 200  
SYFPRGEFYS LVGFGHHIHK QDSHVFNIIA KKFINDTLKG EIVEKAN 247  
(SEQ ID NO:4)

FIG. 1d



MIHLKRTISV	EQLKSVFGQL	SPMNLFLIIL	VGVI AVLPTT	GYDFVLNGLL	50
RTDKSKRYIL	QTSWCINTFN	NLSGFGGLID	IGLRMAFYGK	KGQEKSDLRE	100
VTRFLPYLIS	GLSFISVIAL	IMSHIFHAKA	SVDYYYLVLI	GASMYFPVIY	150
WISGHKGSHY	FGDMPSSTRI	KLGVVSFFEW	GCAAAAFIII	GYLMGIHLPV	200
YKILPLFCIG	CAVGIVSLIP	GGLGSFELVL	FTGFAAEGLP	KETVVAWLLL	250
YRLAYYIIPF	FAGIYFFIHY	LGSQINQRYE	NVPKELVSTV	LQTMVSHLMR	300
ILGAFLIFST	AFFENITYIM	WLQKLGLDPL	QEQLMWQFPG	LLLGVCFILL	350
ARTIDQKVKN	AFPIAIIWIT	LTLFYLNLGH	ISWRLSFWFI	LLLLGLLVIK	400
PTLYKKQFIY	SWEERIKDGI	IIVSLMGVLF	YIAGLLFPPIR	AHITGGSIER	450
LHYIIAWEPI	ALATLILTLV	YLCLVKILQG	KSCQIGDVFN	VDRYKKLLQA	500
YGGSSDSGLA	FLNDKRLYWY	QKNGEDCVAF	QFVIVNNKCL	IMGEPAGDDT	550
YIREAIESFI	DDADKLDYDL	VFYSIGQKLT	LLLHEYGFDF	MKVGEDALVN	600
LETFTLKGK	YKPFERNALNR	VEKDGIFYFEV	VQSPHSQELL	NSLEEISNTW	650
LEGRPEKGFS	LGIFYNKDYFQ	QAPIALVKNA	EHEVVAFANI	MPNYEKSIIS	700
IDLMRHDQKQ	IPNGVMDFLF	LSLFSYYQEK	GYHYFDLGMA	PLSGVGRVET	750
SFAKERMAYL	VYHFGSHFYS	FNGLHKKYKKK	FTPLWSERYI	SCSRSSWLIC	800
AICALLMEDS	KIKIVK	(SEQ ID NO:5)			816

FIG. 1e

MRILGAFLIF	STAFFENITY	IMWLQKLGLD	PLQEQLMWQF	PGLLLGVCFI	50
LLARTIDQKV	KNAFPIAIIW	ITLTLFYLN	GHISWRLSFW	FILLLLGLLV	100
IKPTLYKKQF	IYSWEERIKD	GIIIVSLMGV	LFYIAGLLFP	IRAHITGGS	150
ERLHYIIAWE	PIALATLILT	LVYLCLVKIL	QKSCQIGDV	FNVDYKKLL	200
QAYGGSSDSG	LAFLNDKRLY	WYQKNGEDCV	AFQFVIVNNK	CLIMGEPAGD	250
DTYIREAIES	FIDDADKLDY	DLVFYSIGQK	LTLLLHEYGF	DFMKVGEDAL	300
VNLETFTLKG	NKYKPFERNAL	NRVEKDGIFY	EVVQSPHSQE	LLNSLEEISN	350
TWLEGRPEKG	FSLGYFNKDY	FQQAPIALVK	NAEHEVVAFA	NIMPNYEKSI	400
ISIDLMRHDK	QKIPNGVMDF	LFLSLFSYYQ	EKGHYFDLG	MAPLSGVGRV	450
ETSFAKERMA	YLVYHFGSHF	YSFNGLHKKY	KKFTPLWSER	YISCSRSSWL	500
ICAICALLME	DSKIKIVK	(SEQ ID NO:6)			518

FIG. 1f

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AATTTTGATA TCGAAACAAC AACTTTTGAG GCAATGAAAA AGCACGCGTC ATTATTGGAG      60
N F D I   E T T   T F E   A M K K   H A S   L L E
---->
AAAATATCTG TTGAGCGTTC TTTTATTGAA TTTGATAAAC TTCTATTAGC ACCTTATTGG      120
K I S V   E R S   F I E   F D K L   L L A   P Y W

CGTAAAGGAA TGCTGGCACT AATAGATAGT CATGCTTTTA ATTATCTACC ATGCTTAAAA      180
R K G M   L A L   I D S   H A F N   Y L P   C L K

AATAGGGAAT TACAATTAAG CGCCTTTTTG TCCCAGTTAG ATAAAGATTT TTTATTTGAG      240
N R E L   Q L S   A F L   S Q L D   K D F   L F E

ACATCAGAAC AAGCTTGGGC ATCACTCATC TTGAGTATGG AAGTTGAACA CACAAAGACT      300
T S E Q   A W A   S L I   L S M E   V E H   T K T

TTTTTAAAAA AATGGAAGAC ATCAACTCAC TTTCAAAAAG ATGTTGAGCA TATAGTGGAT      360
F L K K   W K T   S T H   F Q K D   V E H   I V D

GTTTATCGTA TTCGTGAACA AATGGGATTG GCTAAAGAAC ATCTTTATCG TTATGGAAAA      420
V Y R I   R E Q   M G L   A K E H   L Y R   Y G K

ACTATAATAA AACAAGCGGA AGGTATTTCGC AAAGCAAGAG GCTTGATGGT TGATTTTCGAA      480
T I I K   Q A E   G I R   K A R G   L M V   D F E

AAAATAGAAC AACTAGATAG TGAGTTAGCA ATCCATGATA GGCATGAGAT AGTTGTCAAT      540
K I E Q   L D S   E L A   I H D R   H E I   V V N

GGTGGCACCT TAATCAAGAA ATTAGGAATA AAACCTGGTC CACAGATGGG AGATATTATC      600
G G T L   I K K   L G I   K P G P   Q M G   D I I

TCTCAAATTG AATTAGCCAT TGTTTTAGGA CAACTGATTA ATGAAGAAGA GGCTATTTTA      660
S Q I E   L A I   V L G   Q L I N   E E E   A I L

CATTTTGTTA AGCAGTACTT GATGGATTAG AGAGGATTAT ATGAGCGATT TTTTAGTAGA      720
H F V K   Q Y L   M D                               M S D F   L V D
|----->
TGGATTGACT AAGTCGGTTG GTGATAAGAC GGTCTTTAGT AATGTTTCAT TTATCATCCA      780
G L T   K S V G   D K T   V F S   N V S F   I I H

TAGTTTAGAC CGTATTGGGA TTATTGGTGT CAATGGAAC TGGAAAGACAA CACTATTAGA      840
S L D   R I G I   I G V   N G T   G K T T   L L D

TGTTATTTTCG GGTGAATTAG GTTTTGATGG TGATCGTTCC CCTTTTTCAT CAGCTAATGA      900
V I S   G E L G   F D G   D R S   P F S S   A N D

TTATAAGATT GCTTATTTAA AACAAGAACC AGACTTTGAT GATTCTCAGA CAATTTTGGA      960
Y K I   A Y L K   Q E P   D F D   D S Q T   I L D

CACCGTACTT TCTTCTGACT TAAGAGAGAT GGCTTTAATT AAAGAATATG AATTATTGCT      1020
T V L   S S D L   R E M   A L I   K E Y E   L L L

TAATCACTAC GAAGAAAGTA AGCAATCACG TCTAGAGAAA GTAATGGCAG AAATGGATTC      1080
N H Y   E E S K   Q S R   L E K   V M A E   M D S

TTTAGATGCT TGGTCTATTG AGAGCGAAGT CAAAACAGTA TTATCCAAAT TAGGTATTAC      1140
L D A   W S I E   S E V   K T V   L S K L   G I T

TGATTTGCAG TTGTCGGTTG GTGAATTATC AGGAGGATTA CGAAGACGTG TTCAATTAGC      1200
D L Q   L S V G   E L S   G G L   R R R V   Q L A

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GCAAGTATTA	TTAAATGATG	CAGATTTATT	GCTCTTAGAC	GAACCTACTA	ACCACTTAGA	1260
Q V L	L N D A	D L L	L L D	E P T N	H L D	
TATTGACACT	ATTGCATGGT	TAACGAATTT	TTTGAAAAAT	AGTAAAAAGA	CAGTGCTTTT	1320
I D T	I A W L	T N F	L K N	S K K T	V L F	
TATAACTCAT	GATCGTTATT	TTCTAGACAA	TGTTGCAACA	CGTATTTTTG	AATTAGATAA	1380
I T H	D R Y F	L D N	V A T	R I F E	L D K	
GGCACAGATT	ACAGAATATC	AAGGCAATTA	TCAGGATTAT	GTCCGACTTC	GTGCAGAACA	1440
A Q I	T E Y Q	G N Y	Q D Y	V R L R	A E Q	
AGACGAGCGT	GATGCTGCTA	GTTTACATAA	AAAGAAACAG	CTTTATAAAC	AGGAACTAGC	1500
D E R	D A A S	L H K	K K Q	L Y K Q	E L A	
TTGGATGCGT	ACTCAGCCAC	AAGCTCGTGC	AACGAAACAA	CAGGCTCGTA	TTAATCGTTT	1560
W M R	T Q P Q	A R A	T K Q	Q A R I	N R F	
TCAAAATCTA	AAAAACGATT	TACACCAAAC	AAGCGATACA	AGCGATTTGG	AAATGACATT	1620
Q N L	K N D L	H Q T	S D T	S D L E	M T F	
TGAAACAAGT	CGAATTGGGA	AAAAGGTTAT	TAATTTTGAA	AATGTCTCTT	TTTCTTACCC	1680
E T S	R I G K	K V I	N F E	N V S F	S Y P	
AGATAAATCT	ATCTTGAAAG	ACTTTAATTT	GTTAATTCAA	AATAAGACC	GTATTGGCAT	1740
D K S	I L K D	F N L	L I Q	N K D R	I G I	
CGTTGGAGAT	AATGGTGTTG	GAAAGTCAAC	CTTACTTAAT	TTAATTGTTC	AAGATTTACA	1800
V G D	N G V G	K S T	L L N	L I V Q	D L Q	
GCCGGATTCTG	GGTAATGTCT	CTATTGGTGA	AACGATACGT	GTAGGTTACT	TTTCACAACA	1860
P D S	G N V S	I G E	T I R	V G Y F	S Q Q	
ACTTCATAAT	ATGGATGGCT	CAAAACGTGT	TATTAATTAT	TTGCAAGAGG	TTGCAGATGA	1920
L H N	M D G S	K R V	I N Y	L Q E V	A D E	
GGTTAAAACT	AGTGTCTGGTA	CAACAAGTGT	GACAGAACTA	TTGGAACAAT	TTCTCTTTCC	1980
V K T	S V G T	T S V	T E L	L E Q F	L F P	
ACGTTTCGACA	CATGGAACAC	AAATTGCAAA	ATTATCAGGT	GGTGAGAAAA	AAAGACTTTA	2040
R S T	H G T Q	I A K	L S G	G E K K	R L Y	
CCTTTTAAAA	ATCCTGATTG	AAAAGCCTAA	TGTGTTACTA	CTTGATGAGC	CGACAAATGA	2100
L L K	I L I E	K P N	V L L	L D E P	T N D	
CTTAGATATT	GCTACATTAA	CTGTTCTTGA	AAATTTTTTA	CAAGGCTTTG	GTGGTCCTGT	2160
L D I	A T L T	V L E	N F L	Q G F G	G P V	
GATTACAGTT	AGTCACGATC	GTTACTTTTT	AGATAAAGTG	GCTAATAAAA	TTATTGCGTT	2220
I T V	S H D R	Y F L	D K V	A N K I	I A F	
TGAAGATAAC	GATATCCGTG	AATTTTTTGG	TAATTATACT	GATTATTTAG	ATGAAAAAGC	2280
E D N	D I R E	F F G	N Y T	D Y L D	E K A	
ATTTAATGAG	CAAAATAATG	AAGTTATCAG	TAAAAAAGAG	AGTACCAAGA	CAAGTCGTGA	2340
F N E	Q N N E	V I S	K K E	S T K T	S R E	
AAAGCAAAGT	CGTAAAAGAA	TGTCTTACTT	TGAAAAACAA	GAATGGGCGA	CAATTGAAGA	2400
K Q S	R K R M	S Y F	E K Q	E W A T	I E D	
CGATATTATG	ATATTGGAAA	ATACTATCAC	TCGTATAGAA	AATGATATGC	AAACATGTGG	2460

D I M I L E N T I T R I E N D M Q T C G  
 TAGTGATTTT ACAAGGTTAT CTGATTTACA AAAGGAATTA GATGCAAAAA ATGAAGCACT 2520  
 S D F T R L S D L Q K E L D A K N E A L  
 TCTAGAAAAG TATGACCGTT ATGAGTACCT TAGTGAGTTA GACACATGAT TATCCGTCGG 2580  
 L E K Y D R Y E Y L S E L D T M I I R P  
 |---->  
 ATTATTAAAA ATGATGACCA AGCAGTTGCA CAATTAATTC GACAAAGTTT ACGCGCTAT 2640  
 I I K N D D Q A V A Q L I R Q S L R A Y  
 GATTTAGATA AACCTGATAC AGCATATTCA GACCCTCACT TAGATCATTT GACCTCATAC 2700  
 D L D K P D T A Y S D P H L D H L T S Y  
 TACGAAAAAA TAGAGAAGTC AGGATTCTTT GTCATTGAGG AGAGAGATGA GATTATTGGC 2760  
 Y E K I E K S G F F V I E E R D E I I G  
 TGTGGCGGCT TTGGTCCGCT GAAAAATCTA ATTGCAGAGA TGCAGAAGGT GTACATTGCA 2820  
 C G G F G P L K N L I A E M Q K V Y I A  
 GAACGTTTCC GTGGTAAGGG GCTTGCTACT GATTTAGTGA AAATGATTGA AGTAGAAGCT 2880  
 E R F R G K G L A T D L V K M I E V E A  
 CGAAAAATTG GGTATAGACA ACTTTATTTA GAGACAGCCA GTACTTTGAG TAGGGCAACT 2940  
 R K I G Y R Q L Y L E T A S T L S R A T  
 GCGGTTTATA AGCATATGGG ATATTGTGCC TTATCGCAAC CAATAGCAAA TGATCAAGGT 3000  
 A V Y K H M G Y C A L S Q P I A N D Q G  
 CATACAGCTA TGGATATTTG GATGATTAAA GATTTATAAG TTGAAAGTGG ATTAGTGAAC 3060  
 H T A M D I W M I K D L  
 ATGGATTAAT TATTTTGAGA TAAGAGGAAA GAAAGGAGA CATATATGGC ATATATTTGG 3120  
 M A Y I W  
 |---->  
 TCTTATTTGA AAAGGTACCC CAATTGGTTA TGGCTTGATT TACTAGGAGC TATGCTTTTT 3180  
 S Y L K R Y P N W L W L D L L G A M L F  
 GTGACGGTTA TCCTAGGAAT GCCACAGCC TTAGCGGGTA TGATTGATAA TGGCGTTACA 3240  
 V T V I L G M P T A L A G M I D N G V T  
 AAAGGTGATC GGA CTGGAGT TTATCTGTGG ACGTTCATCA TGTTTATATT TGTTGTACTA 3300  
 K G D R T G V Y L W T F I M F I F V V L  
 GGTATTATTG GCGTATTAC GATGGCTTAC GCATCTAGTC GCTTAACGAC AACAATGATT 3360  
 G I I G R I T M A Y A S S R L T T T M I  
 AGAGATATGC GTAATGATAT GTATGCTAAG CTTCAAGAAT ACTCCCATCA TGAATATGAA 3420  
 R D M R N D M Y A K L Q E Y S H H E Y E  
 CAGATAGGTG TATCTTCACT AGTGACACGT ATGACAAGCG ATACTTTTGT TTTGATGCAA 3480  
 Q I G V S S L V T R M T S D T F V L M Q  
 TTTGCTGAAA TGTCTTTACG TTTAGGCCTA GTAACCTCTA TGGTAATGAT TTTTAGCGTG 3540  
 F A E M S L R L G L V T P M V M I F S V  
 GTTATGATAC TAATTACGAG TCCATCTTTG GCTTGCTTGG TAGCGGTTGC GATGCCTCTT 3600  
 V M I L I T S P S L A W L V A V A M P L  
 TTGGTAGGAG TCGTTTTATA TGTAAGCTATA AAAACAAAAC CTTTATCTGA AAGACAACAG 3660  
 L V G V V L Y V A I K T K P L S E R Q Q

ACTATGCTTG ATAAAATCAA TCAATATGTT CGTGAAAATT TAACAGGGTT ACGCGTTGTT	3720
T M L D K I N Q Y V R E N L T G L R V V	
AGAGCCTTTG CAAGAGAGAA TTTTCAATCA CAAAAATTTT AAGTCGCTAA CCAACGTTAC	3780
R A F A R E N F Q S Q K F Q V A N Q R Y	
ACAGATACTT CAACTGGTCT TTTTAAATTA ACAGGGCTAA CAGAACCACT TTTCGTTCAA	3840
T D T S T G L F K L T G L T E P L F V Q	
ATTATTATTG CAATGATTGT GGCTATCGTT TGGTTTGCTT TGGATCCCTT ACAAAGAGGT	3900
I I I A M I V A I V W F A L D P L Q R G	
GCTATTAAAA TAGGGGATTT AGTTGCTTTT ATCGAATATA GCTTCCATGC TCTCTTTTCA	3960
A I K I G D L V A F I E Y S F H A L F S	
TTTTTGCTAT TTGCCAATCT TTTTACTATG TATCCTCGTA TGGTGGTATC AAGCCATCGT	4020
F L L F A N L F T M Y P R M V V S S H R	
ATTAGAGAGG TGATGGATAT GCCAATCTCT ATCAATCCTA ATGCCGAAGG TGTTACGGAT	4080
I R E V M D M P I S I N P N A E G V T D	
ACGAAACTTA AAGGGCATT T AGAATTTGAT AATGTAACAT TCGCTTATCC AGGAGAAACA	4140
T K L K G H L E F D N V T F A Y P G E T	
GAGAGTCCCG TTTTGCATGA TATTTCTTTT AAAGCTAAGC CTGGAGAAAC AATTGCTTTT	4200
E S P V L H D I S F K A K P G E T I A F	
ATTGGTTCAA CAGGTT CAGG AAAATCTTCT CTTGTTAATT TGATTCCACG TTTTATGAT	4260
I G S T G S G K S S L V N L I P R F Y D	
GTGACACTTG GAAAAATCTT AGTAGATGGA GTTGATGTAA GAGATTATAA CCTTAAATCA	4320
V T L G K I L V D G V D V R D Y N L K S	
CTTCGCCAAA AGATTGGATT TATCCCCCAA AAAGCTCTTT TATTTACAGG GACAATAGGA	4380
L R Q K I G F I P Q K A L L F T G T I G	
GAGAATTTAA AATATGGAAA AGCTGATGCT ACTATTGATG ATCTTAGACA AGCGGTTGAT	4440
E N L K Y G K A D A T I D D L R Q A V D	
ATTTCTCAAG CTAAAGAGTT TATTGAGAGT CACCAAGAAG CCTTTGAAAC GCATTTAGCT	4500
I S Q A K E F I E S H Q E A F E T H L A	
GAAGGTGGGA GCAATCTTTC TGGGGGTCAA AAACAACGGT TATCTATTGC TAGGGCTGTT	4560
E G G S N L S G G Q K Q R L S I A R A V	
GTAAAGATC CAGATTTATA TATTTTTGAT GATTCATTTT CTGCTCTCGA TTATAAGACA	4620
V K D P D L Y I F D D S F S A L D Y K T	
GACGCTACTT TAAGAGCGCG TCTAAAAGAA GTAACCGGTG ATTCTACAGT TTTGATAGTT	4680
D A T L R A R L K E V T G D S T V L I V	
GCTCAAAGGG TGGGTACGAT TATGGATGCT GATCAGATTA TTGTCCTTGA TGAAGGCGAA	4740
A Q R V G T I M D A D Q I I V L D E G E	
ATTGTCGGTC GTGGTACCCA CGCTCAATTA ATAGAAAATA ATGCTATTTA TCGTGAAATC	4800
I V G R G T H A Q L I E N N A I Y R E I	
GCTGAGTCAC AACTGAAGAA CCAAACTTA TCAGAAGGAG AGTGATTGTA TGAGAAAAAA	4860
A E S Q L K N Q N L S E G E M R K K	
----->	

ATCTGTTTTT	TTGAGATTAT	GGTCTTACCT	AACTCGCTAC	AAAGCTACTC	TTTTCTTAGC	4920
S V F	L R L W	S Y L	T R Y	K A T L	F L A	
GATTTTTTTG	AAAGTTTTAT	CTAGTTTTAT	GAGTGTTCTG	GAGCCTTTTA	TTTAGGGTT	4980
I F L	K V L S	S F M	S V L	E P F I	L G L	
AGCGATAACA	GAGTTGACTG	CTAACCTTGT	TGATATGGCT	AAGGGAGTTT	CTGGGGCAGA	5040
A I T	E L T A	N L V	D M A	K G V S	G A E	
ATTGAACGTT	CCTTATATTG	CTGGTATTTT	GATTATTTAT	TTTTTCAGAG	GTGTTTTCTA	5100
L N V	P Y I A	G I L	I I Y	F F R G	V F Y	
TGAATTAGGT	TCTTATGGCT	CAAATT	(SEQ ID NO:7)			5126
E L G	S Y G S	N				

FIG. 2a

NFDIETTTTFF	AMKKHASLLE	KISVERSFIE	FDKLLLAPYW	RKGMLALIDS	50
HAFNYLPCLK	NRELQLSAFL	SQLDKDFLFE	TSEQAWASLI	LSMEVEHTKT	100
FLKKWKTSTH	FQKDVEHIVD	VYRIREQMGL	AKEHLYRYGK	TIKQAEGIR	150
KARGLMVDFF	KIEQLDSELA	IHDRHEIVVN	GGTLIKKLG	KPGPQMGDII	200
SQIELAIVLG	QLINEEEAIL	HFVKQYLM	(SEQ ID NO:8)		229

FIG. 2b

MSDFLVDGLT	KSVGDKTVFS	NVSFIIHSLD	RIGIIGVNGT	GKTTLLDVIS	50
GELGFDGDRS	PFSSANDYKI	AYLKQEPDFD	DSQTILDTVL	SSDLREMAI	100
KEYELLLNHY	EESKQSRLEK	VMAEMDSLDA	WSIESEVKT	LSKLGITDLQ	150
LSVGELSGGL	RRRVQLAQVL	LNDADLLLLD	EPTNHLIDIT	IAWLTNFLKN	200
SKKTVLFITH	DRYFLDNVAT	RIFELDKAQI	TEYQGNQDY	VLRAEQDER	250
DAASLHKKKQ	LYKQELAWMR	TQPQARATKQ	QARINRFQNL	KNDLHQTSDT	300
SDLEMTFETS	RIGKKVINFE	NVSFSYPDKS	ILKDFNLLIQ	NKDRIGIVGD	350
NGVGKSTLLN	LIVQDLQPDS	GNVSIGETIR	VGYFSQQLHN	MDGSKRVINY	400
LQEVADDEVKT	SVGTTSVTEL	LEQFLFPRST	HGTQIAKLSG	GEKKRLYLLK	450
ILIEKPNVLL	LDEPTNDLDI	ATLTVLENFL	QGFGGPVITV	SHDRYFLDKV	500
ANKIIAFEDN	DIREFFGNYT	DYLDEKAFNE	QNNEVISKKE	STKTSREKQS	550
RKRMSYFEKQ	EWATIEDDIM	ILENTITRIE	NDMQTCGSDF	TRLSDLQKEL	600
DAKNEALLEK	YDRYEYLSL	DT	(SEQ ID NO:9)		622

FIG. 2c

MIIRPIIKND	DQAVAQLIRQ	SLRAYDLDP	DTAYSDPHLD	HLTSYYEKIE	50
KSGFFVIEER	DEIIGCGGFG	PLKNLIAEMQ	KVYIAERFRG	KGLATDLVKM	100
IEVEARKIGY	RQLYLETAST	LSRATAVYKH	MGYCALSQPI	ANDQGHTAMD	150
IWMIKDL	(SEQ ID NO:10)				157

FIG. 2d

MAYIWSYLKR	YPNWLWLDLL	GAMLFVTVIL	GMPTALAGMI	DNGVTKGDRT	50
GVYLWTFIMF	IFVVLGIIGR	ITMAYASSRL	TTMIRDMRN	DMYAKLQEYS	100
HHEYEQIGVS	SLVTRMTSDT	FVLMQFAEMS	LRLGLVTPMV	MIFSVVMILI	150
TSPSLAWLVA	VAMPLLVGTV	LYVAIKTKPL	SERQQTMLDK	INQYVRENLT	200
GLRVVRAFAR	ENFQSQKFQV	ANQRYTDTST	GLFKLTGLTE	PLFVQIIIAM	250
IVAIVWFALD	PLQRGAIKIG	DLVAFIEYSF	HALFSFLLFA	NLFTMYPRMV	300
VSSHRIREVM	DMPISINPNA	EGVTDTKLKG	HLEFDNVTFA	YPGETESPVL	350
HDISFKAKPG	ETIAFIGSTG	SGKSSLVNLI	PRFYDVTLGK	ILVDGVDVRD	400
YNLKSLRQKI	GFIPQKALLF	TGTIGENLKY	GKADATIDDL	RQAVDISQAK	450
EFIESHQEAF	ETHLAEGGSN	LSGGQKQRLS	IARAVVKDPD	LYIFDDSFSA	500
LDYKTDATLR	ARLKEVTGDS	TVLIVAQRVG	TIMDADQIIV	LDEGEIVGRG	550
THAQLIENNA	IYREIAESQL	KNQNLSEGE	(SEQ ID NO:11)		579

FIG. 2e

MRKKSFLRL	WSYLTRYKAT	LFLAIFLKV	SSFMSVLEPF	ILGLAITELT	50
ANLVDMAKGV	SGAELNVPYI	AGILIIYFFR	GVFYELGSYG	SN	92
(SEQ ID NO:12)					

FIG. 2f



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AATTTGGAAG TGCTCTATCA ACAGTTGAAG TAAAGGAGAT TATTAGTGAA GAAAACATAT      60
  F G S   A L S   T V E V   K E I   I S E   E N I W
  ---->
GGTTATATCG GCTCAGTTGC TGCCATTTTA CTAGCTACTC ATATTGGAAG TTACCAACTT      120
  L Y R   L S C   C H F T   S Y S   Y W K   L P T W

GGTAAGCATC ATATGGGTCT AGCAACAAAG GACAATCAGA TTGCCTATAT TGATGACAGC      180
          M G L   A T K   D N Q I   A Y I   D D S
          |---->
AAAGGTAAGG CAAAAGCCCC TAAAACAAAC AAAACGATGG ATCAAATCAG TGCTGAAGAA      240
  K G K A   K A P   K T N   K T M D   Q I S   A E E

GGCATCTCTG CTGAACAGAT CGTAGTCAAA ATTACTGACC AAGGCTATGT GACCTCACAC      300
  G I S A   E Q I   V V K   I T D Q   G Y V   T S H

GGTGACCATT ATCATTTTTTA CAATGGGAAA GTTCCTTATG ATGCGATTAT TAGTGAAGAG      360
  G D H Y   H F Y   N G K   V P Y D   A I I   S E E

TTGTTGATGA CGGATCCTAA TTACCGTTTT AAACAATCAG ACGTTATCAA TGAAATCTTA      420
  L L M T   D P N   Y R F   K Q S D   V I N   E I L
          |---->
GACGGTTACG TTATTAAAGT CAATGGCAAC TATTATGTTT ACCTCAAGCC AGGTAGTAAG      480
  D G Y V   I K V   N G N   Y Y V Y   L K P   G S K

CGCAAAAACA TTCGAACCAA ACAACAAATT GCTGAGCAAG TAGCCAAAGG AACTAAAGAA      540
  R K N I   R T K   Q Q I   A E Q V   A K G   T K E

GCTAAAGAAA AAGGTTTAGC TCAAGTGGCC CATCTCAGTA AAGAAGAAGT TCGGGCAGTC      600
  A K E K   G L A   Q V A   H L S K   E E V   A A V

AATGAAGCAA AAAGACAAGG ACGCTATACT ACAGACGATG GCTATATTTT TAGTCCGACA      660
  N E A K   R Q G   R Y T   T D D G   Y I F   S P T

GATATCATTG ATGATTTAGG AGATGCTTAT TTAGTACCTC ATGGTAATCA CTATCATTAT      720
  D I I D   D L G   D A Y   L V P H   G N H   Y H Y

ATTCTTAAAA AGGATTTGTC TCCAAGTGAG CTAGCTGCTG CACAAGCCTA CTGGAGTCAA      780
  I P K K   D L S   P S E   L A A A   Q A Y   W S Q

AAACAAGGTC GAGGTGCTAG ACCGTCTGAT TACCGCCCGA CACCAGCCCC AGGTCGTAGG      840
  K Q G R   G A R   P S D   Y R P T   P A P   G R R

AAAGCCCCAA TTCCTGATGT GACGCCTAAC CCTGGACAAG GTCATCAGCC AGATAACGGT      900
  K A P I   P D V   T P N   P G Q G   H Q P   D N G

GGCTATCATC CAGCGCCTCC TAGGCCAAAT GATGCGTCAC AAAACAAACA CCAAAGAGAT      960
  G Y H P   A P P   R P N   D A S Q   N K H   Q R D

GAGTTTAAAG GAAAAACCTT TAAGGAACTT TTAGATCAAC TACACCGTCT TGATTTGAAA      1020
  E F K G   K T F   K E L   L D Q L   H R L   D L K

TACCGTCATG TGGAAGAAGA TGGGTTGATT TTTGAACCGA CTCAAGTGAT CAAATCAAAC      1080
  Y R H V   E E D   G L I   F E P T   Q V I   K S N

GCTTTTGGGT ATGTGGTGCC TCATGGAGAT CATTATCATA TTATCCCAAG AAGTCAGTTA      1140
  A F G Y   V V P   H G D   H Y H I   I P R   S Q L

TCACCTCTTG AAATGGAATT AGCAGATCGA TACTTAGCTG GCCAAACTGA GGACAATGAC      1200
  S P L E   M E L   A D R   Y L A G   Q T E   D N D

TCAGGTTTCA AGCACTCAAA ACCATCAGAT AAAGAAGTGA CACATACCTT TCTTGGTCAT      1260

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S G S E H S K P S D K E V T H T F L G H  
 CGCATCAAAG CTTACGGAAA AGGCTTAGAT GGTAACCAT ATGATACGAG TGATGCTTAT 1320  
 R I K A Y G K G L D G K P Y D T S D A Y  
 GTTTTATAGTA AAGAATCCAT TCATTCAAGT GATAAATCAG GAGTTACAGC TAAACACGGA 1380  
 V F S K E S I H S V D K S G V T A K H G  
 GATCATTTCC ACTATATAGG ATTTGGAGAA CTTGAACAAT ATGAGTTGGA TGAGGTCGCT 1440  
 D H F H Y I G F G E L E Q Y E L D E V A  
 AACTGGGTGA AAGCAAAAAGG TCAAGCTGAT GAGCTTGCTG CTGCTTTGGA TCAGGAACAA 1500  
 N W V K A K G Q A D E L A A A L D Q E Q  
 GGCAAGAAA AACCCTCTT TGACACTAAA AAAGTGAGTC GCAAGTAAC AAAAGATGGT 1560  
 G K E K P L F D T K K V S R K V T K D G  
 AAAGTGGGCT ATATGATGCC AAAAGATGGT AAGGACTATT TCTATGCTCG TGATCAACTT 1620  
 K V G Y M M P K D G K D Y F Y A R D Q L  
 GATTTGACTC AGATTGCCTT TGCCGAACAA GAACTAATGC TTAAAGATAA GAAGCATTAC 1680  
 D L T Q I A F A E Q E L M L K D K K H Y  
 CGTTATGACA TTGTTGACAC AGGTATTGAG CCACGACTTG CTGTAGATGT GTCAAGTCTG 1740  
 R Y D I V D T G I E P R L A V D V S S L  
 CCGATGCATG CTGGTAATGC TACTTACGAT ACTGGAAGTT CGTTTGTTAT CCCACATATT 1800  
 P M H A G N A T Y D T G S S F V I P H I  
 GATCATATCC ATGTCGTTCC GTATTCATGG TTGACGCGCG ATCAGATTGC AACAGTCAAG 1860  
 D H I H V V P Y S W L T R D Q I A T V K  
 TATGTGATGC AACACCCCGA AGTTCGTCCG GATGTATGGT CTAAGCCAGG GCATGAAGAG 1920  
 Y V M Q H P E V R P D V W S K P G H E E  
 TCAGGTTCCG TCATTCCAAA TGTTACGCTT CTTGATAAAC GTGCTGGTAT GCCAACTGG 1980  
 S G S V I P N V T P L D K R A G M P N W  
 CAAATTATCC ATTCTGCTGA AGAAGTTCAA AAAGCCCTAG CAGAAGGTCG TTTTGCAACA 2040  
 Q I I H S A E E V Q K A L A E G R F A T  
 CCAGACGGCT ATATTTTCGA TCCACGAGAT GTTTTGCCCA AAGAACTTT TGTATGGAAA 2100  
 P D G Y I F D P R D V L A K E T F V W K  
 GATGGCTCCT TTAGCATCCC AAGAGCAGAT GGCAGTTCAT TGAGAACCAT TAATAAATCT 2160  
 D G S F S I P R A D G S S L R T I N K S  
 GATCTATCCC AAGCTGAGTG GCAACAAGCT CAAGAGTTAT TGGCAAAGAA AAATACTGGT 2220  
 D L S Q A E W Q Q A Q E L L A K K N T G  
 GATGCTACTG ATACGGATAA ACCCAAAGAA AAGCAACAGG CAGATAAGAG CAATGAAAAC 2280  
 D A T D T D K P K E K Q Q A D K S N E N  
 CAACAGCCAA GTGAAGCCAG TAAAGAAGAA AAAGAATCAG ATGACTTTAT AGACAGTTTA 2340  
 Q Q P S E A S K E E K E S D D F I D S L  
 CCAGACTATG GTCTAGATAG AGCAACCCTA GAAGATCATA TCAATCAATT AGCACAAAAA 2400  
 P D Y G L D R A T L E D H I N Q L A Q K  
 GCTAATATCG ATCCTAAGTA TCTCATTTTC CAACCAGAAG GTGTCCAATT TTATAATAAA 2460  
 A N I D P K Y L I F Q P E G V Q F Y N K

AATGGTGAAT TGGTAACTTA TGATATCAAG ACACTTCAAC AAATAAACCC TTAACCAAAA 2520  
 N G E L V T Y D I K T L Q Q I N P  
 GAAGATCTCA TTGTTAAAGC ACTGCTTTGT CAAAGCAAGT TACGGTGATT TTGAAGTCAT 2580  
 TCTATGTAAC GAGTAGTGAT AAAAGTTGGA TAATAGCGGT TTTCTTTTGC AAAGAAATGG 2640  
 TATCCATGTT AGAATAGTAA AAAAAAGAGGA GGATTCTTGG ACTAATGTCA AATAAGTAGA 2700  
 CAGAAACTG TGTATTTTTA TTGCGTTAAA ATAATTTTCT TCTTTCTGAT TAGGGGTTAG 2760  
 .K I A N F Y N E E K Q N P T L  
 TCCTAGATTA GCCGTATGTG GGTGTAATT GTTATAAAAA TTCTCAATGT ATTCAAAGCA 2820  
 G L N A T H P N Y N N Y F N E I Y E F C  
 GTCTAATTGA ACCTGTTTGA TATTTTGATA ATGTTTTCGG TTGATTTGTC TATGCTTTAA 2880  
 D L Q V Q K I N Q Y H K R N I Q R H K L  
 ATACTTGAAA AATGCTTCAG TTACGGCATT ATCATAAGGA TATCCAGGAT TAGAAAAAGA 2940  
 Y K F F A E T V A N D Y P Y G P N S F S  
 ATGCATGATA TTGGCACTGC ACCCTAATAG TGAGACGCAA GAAAAACACT TTTAGGCAAT 3000  
 H M A I  
 <----|  
 CAGTTTTCTG TACTGTACAG GCGACTGGTC GTTTAATCTC TGTGAATTC TAGTTTCATT 3060  
 L K R Y Q V P S Q D N L R Q Q I R T E N  
 ATAAAATGTA ATGTAATTTT TAACAATATT TGTTATACTA TCTTTGTTGT ATTTTCTCCT 3120  
 Y F T I Y N K V I N T I S D K N Y K R R  
 ATTATGGAAA TAAAAGGTTT CAGTCTTTAG GACGGTGTGA AACCATTCAA TACAGGCATT 3180  
 N H F Y F T E T K L V T H F W E I C A N  
 ATCTGCAGGT GTTCCTTTTC GAGACATTGA GCGGATAATG TCTTTTTCCG TGCAAGCCTG 3240  
 D A P T G K R S M S R I I D K E T C A Q  
 GTAGTAAGCC ATAGAAGTAT ACACTGAGCC TTGGTCACTG TGTAAGATTG CTCCTTTATT 3300  
 Y Y A M  
 <----|  
 TAGGCAATTT TAACTGATTA AGGGTGTCTA GTACAAAATC CGTGTCTGA CAATCTGAGA 3360  
 K P L K L Q N L T D L V F D T D Q C D S  
 TAGTGTAAAG TATAATTTCT CGGTTATAGA GATTCATAAT TGATGAGAGA TACAATTTAC 3420  
 I T Y A I I E R N Y L N M I S S L Y L K  
 AGTTACCGAA ATATAGGTAG GTAATATCTG TTACGAGCTT TTCCTTAGGC TTATCGGCAT 3480  
 C N G F Y L Y T I D T V L K E K P K D A  
 GGAAATCCCG ACTCAATTTA TTATCTGTGA AATAATAAGC TTTACCCAAA TTGGGAACTT 3540  
 H G D R S L K N D T L Y Y A K G L N P V  
 TCTTGGTACG TGTCCGACAA AGCCAGCCAT TATTTTTCAT GATACGATAG ACTTTCTTTG 3600  
 K K T R T R C L W G N N K M I R Y V K K  
 TATTAACAGT CAATCCGTGG ATTTTGTGTA GCAATCGTGT AATGGTACGA TAGCCATAAA 3660  
 T N V T L G H I K K L L R T I T R Y G Y  
 TAAAGTGATT CTCCATACAG AGCTGTTCAA TTAATTCAAT AAGGTCATCT TTTTTGCGG 3720  
 I F H N E M  
 <----|

CTTCTCATAC TCCTTTTTCC AACGGTAATA GGTGACCGC TTGACCTTAA AACAGTCTAG 3780  
 AATGAAACT ATCGGGTAGT TGTTTTTATA GTCTTCCACA AGCTTGATAA GACTTACTTT 3840  
 ATCGATTTCC TTATCAAGCC TCGATACTTT TTTAAGAGGT CAACCTGTAA TTGTAATTGT 3900  
 I S K R I L G R Y K K L L D V Q L Q L Q  
 TCCACTTCAG ACAGATGTTT CAAGCCTTTA CCGTAGGTAT ATTGCTTGCC AACACCTTGA 3960  
 E V E S L H E L G K G Y T Y Q K G V G Q  
 TGAAAACGAT AAAGCTCCTC GTTTTCGTAC CATTTCATCC AAGTATAGAT TTGACTATTA 4020  
 H F R Y L E E N E Y W K M W T Y I Q S N  
 TTTTGTATGC CTAAAGTCTC CATAATAACT CTGTTAGACT TGCCTGCTTT CTTCATATCG 4080  
 N K I G L T E M I V R N S K G A K K M D  
 ATGCAAGCCA GCTTAGTTTC CCATGAATAT GCTTTTTTAA CCATAATAAA ACATTCCTGT 4140  
 I C A L K T E W S Y A K K V M  
 TTCTAGTTTA CTAAATTTCA ACAGGAGTGT TTTTCTTTTG TCTCATTTTA GGGATTCAGT 4200  
 GCCTATTGTT GTCATCAATT ATTTTCTAA ATTCCCCGGA CTAAATTGT GACCCTTGGT 4260  
 CGGAATGAAA GAGAAGTGTT CCTTCAATCT TTCTTTTATT AAGTGAAAAG GCAACACTTT 4320  
 TCTGTACAAC ATTTATAAAG TGTTTTTCTA GGCAATTAAT CTTTGTAGTCA TTGGTGTTTG 4380  
 . A I L R K T M P T Q  
 GTAGTTGAGA CTACCATGAA TGCGGTGGTA ATTCCACCAA TGAACATAGT CTTTAGTCTT 4440  
 Y N L S G H I R H Y N W W H V Y D K T K  
 AAGAGCTAGT TCTTCCAGCA ATTGAAAGGT TTCTTGATAA ACAAATTCAA TTTTGAAAGC 4500  
 L A L E E L L Q F T E Q Y V F E I K F A  
 ACGATACGTA CTTTCAGCTA CGGCATTGTC ATAAGGATAA CCAGCCTGAC TAAGCGAACG 4560  
 R Y T S E A V A N D Y P Y G A Q S L S R  
 TGTGATTCCA AAGGCTTCCA ATATTTTCATC AATTAAGTGA TTATCAAACCT CTTTGCCACG 4620  
 T I G F A E L I E D I L Q N D F E K G R  
 ATCTGAATGG AACATCTTGA CTTTGGTCAG GCGTAAGGG ATGCTTTGTA TGGCTTGCTT 4680  
 D S H F M K V K T L A Y P I S Q I A Q K  
 AACGAGTTCA GCGGTCTTGT GCCAACCAAG AGACAGGCCG ATGATTTTAC GGTGTATAG 4740  
 V L E A T K H W G L S L G I I E R N Y L  
 GTCAATGATG AGGCAAACAT AAGCCCAACG ATTGCCTACA CGAACATAGG TTAAGTCAGT 4800  
 D I I L C V Y A W R N G V R V Y T L D T  
 GACTAAGGCT TGTAAGTGGT TTTCTTGCTT AAATTGCCTG TCTAAGTGGT TGGGAATAGG 4860  
 V L A Q L P R E Q K F Q R D L H N P I P  
 GGCTTCATTC TTGCCTCTAG AATGTGGTTT GAAGGTGGCT TTCTGATAAA CAGAAACCAA 4920  
 A E N K G R S H P K F T A K Q Y V S V L  
 ATTGAGTCGC TTCATAATGC GTCGAATCCG ACGACGTGAA AGTGTGATAC CTTGCTTATT 4980  
 N L R K M I R R I R R R S L T I G E N N  
 CAAGCATATT TTGATTTTTC TGGATCCGTA TCTAGACTCG CTATCGAGAA AAATTCTTTT 5040  
 L C I K I K R S G Y R S E S D L F I R K

```

AATAGTTTCT TCAAACCTCCG TTTCAGATAC TGA CTCCACG GCTTGATAGT AATAACTTGA 5100
  I T E E F E T E S V S E V A Q Y Y Y S S
GTGTGGCATA TTCAGCCAGC GACACATCTT TGAAATGCTG TATTTATCCT TATTAGCAGT 5160
  H P M N L W R C M K S I S Y K D K N A T
GATTATTTCC CTTTTGTGC CATAATCACC GCTGCTTGCT TTAGGATATC TAATT 5215
  I I E R K T G Y D G S S A K P Y R I
(SEQ ID NO:13)

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FIG. 3a

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FGSALSTVEV KEIISEENIW LYRLSCCHFT SYSYWKLPWT 40
(SEQ ID NO:14)

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FIG. 3b

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MGLATKDNQI AYIDDSKGKA KAPKTNKTMD QISAEEGISA EQIVVKITDQ 50
GYVTSHGDHY HFYNGKVPYD AIISEELLMT DPNYRFKQSD VINEILDGYV 100
IKVNGNYVVY LKPGSKRKNI RTKQQIAEQV AKGTKEAKEK GLAQVAHLSK 150
EEVAAVNEAK RQGRYTTDDG YIFSPTDIID DLGDAYLVPH GNHYHYIPKK 200
DLSPSELAAA QAYWSQKQGR GARPSDYRPT PAPGRRKAPI PDVTPNPGQG 250
HQPNDGGYHP APPRPNDASQ NKHQ RDEFKG KTFKELLDQL HRLDLKYRHV 300
EEDGLIFEPT QVIKSNAFGY VVPHGDHYHI IPRSQLSPL E MELADRYLAG 350
QTEDNDSGSE HSKPSDKEVT HTFLGHRIKA YGKGLDGKPY DTSDAYVFSK 400
ESIHSVDSKG VTAKHGDH FH YIGFGELEQY ELDEVANWVK AKGQADELAA 450
ALDQEQGKEK PLFDTKKVSR KVT KDGVGY MMPKDGKDYF YARDQLDLTQ 500
IAFAEQELML KDKKHRYDI VDTGIEPRLA VDVSSLPMHA GNATYDTGSS 550
FVIPHIDHIH VVPYSWLTRD QIATVKYVMQ HPEVRPDVWS KPGHEESGSV 600
IPNVTPLDKR AGMPNWQIIH SAEVQKALA EGRFATPDGY IFDPRDVLAK 650
ETFVWKDGSF SIPRADGSSL RTINKSDL SQ AEWQQAQELL AKKNTGDATD 700
TDKPKEKQQA DKSNNQQPS EASKEEKESD DFIDSLPDYG LDRATLEDHI 750
NQLAQKANID PKYLIFQPEG VQFYNNKNGEL VTYDIKTLQQ INP 793
(SEQ ID NO:15)

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FIG. 3c

MTDPNYRFBKQ	SDVINEILDG	YVIKVNNGNY	VYLKPGSKRK	NIRTKQQIAE	50
QVAKGTKEAK	EKGLAQVAHL	SKEEVAANE	AKRQGRYTTD	DGYIFSPTDI	100
IDDLGDAYLV	PHGNHYHYIP	KKDLSPSELA	AAQAYWSQKQ	GRGARPSDYR	150
PTPAPGRRKA	PIPDVTPNPG	QGHQPDNGGY	HPAPPRPND	SONKHQRDEF	200
KGKTFKELLD	QLHRLDLKYR	HVEEDGLIFE	PTQVIKSNAF	GYVVPBGDHY	250
HIIPRSQSLP	LEMELADRYL	AGQTEDNDG	SEHSKPSDKE	VTHTFLGHRI	300
KAYGKGLDGK	PYDTSDAYVF	SKESIHSVDK	SGVTAKHGDH	FHYIGFGELE	350
QYELDEVANW	VKAKGQADEL	AAALDQEQGK	EKPLFDTKKV	SRKVTKDGKV	400
GYMMPKDGKD	YFYARDQLDL	TQIAFAEQEL	MLKDKKHRYR	DIVDTGIEPR	450
LAVDVSSLPM	HAGNATYDTG	SSFVIPHIDH	IHVVPYSWLT	RDQIATVKYV	500
MQHPEVRPDV	WSKPGHEESG	SVIPNVTPLD	KRAGMPNWQI	IHSAEEVQKA	550
LAEGRFATPD	GYIFDPRDVL	AKETFVWKDG	SFSIPRADGS	SLRTINKSDL	600
SQAEWQQAQE	LLAKKNTGDA	TDTDKPKEKQ	QADKSNENQQ	PSEASKEEKE	650
SDDFIDSLPD	YGLDRATLED	HINQLAQKAN	IDPKYLIFQP	EGVQFYNNKG	700
ELVTYDIKTL	QQINP	(SEQ ID NO:16)			715

FIG. 3d

MHSFSNPGYP	YDNAVTEAFF	KYLKHRQINR	KHYQNIKQVQ	LDCFEYIENF	50
YNNYNPHTAN	LGLTPNQKEE	NYFNAIK	(SEQ ID NO:17)		77

FIG. 3e

MAYYQACTEK	DIIRMSRKG	TPADNACIEW	FHTVLKTETF	YFHNRRKYNK	50
DSITNIVKNY	ITFYNETRIQ	QRLNDQSPVQ	YRKLIA	(SEQ ID NO:18)	86

FIG. 3f

MENHFIYGYR	TITRLLKKIH	GLTVNTKKVY	RIMKNNGWLC	RTRTKKVPNL	50
GKAYYLTDNK	LSRDFHADKP	KEKLVTDITY	LYFGNCKLYL	SSIMNLYNRE	100
IIAYTISDCQ	DTDFVLDTLN	QLKLPK	(SEQ ID NO:19)		126

FIG. 3g

MVKKAYSWET KLACIDMKKA GKSNRVIMET LGIKNNSQIY TWMKWYENEE 50  
 LYRFHQGVGK QYTYGKGLEH LSEVEQLQLQ VDLLKKYRGL IRKSIK 96  
 (SEQ ID NO:20)

FIG. 3h

IRYPKASSGD YGTKREIITA NKDKYSISKM CRWLNMPHSS YYYQAVESVS 50  
 ETEFEETIKR IFLDSESRYG SRKIKICLNN EGITLSRRRI RRIMKRLNLV 100  
 SVYQKATFKP HSRGKNEAPI PNHLDRQFKQ ERPLQALVTD LTYVRVGNRW 150  
 AYVCLIIDLY NREIIGLSLG WHKTAELVKQ AIQSIPYALT KVKMFHSDRG 200  
 KEFDNQLIDE ILEAFGITRS LSQAGYPYDN AVAESTYRAF KIEFVYQETF 250  
 QLLEELALKT KDYVHWWNYH RIHGSLNYQT PMTKRLIA (SEQ ID NO:21) 288

FIG. 3i

AATTTGAAAG CAGAATTATC TGTAGAAGAT GAGCAATATA CAGCAACAGT TTATGGTAAA 60  
 N L K A E L S V E D E Q Y T A T V Y G K  
 ---->  
 TCTGCTCATG GTTCAACACC ACAAGAAGGT GTTAATGGGG CGACTTATTT AGCTCTTTAT 120  
 S A H G S T P Q E G V N G A T Y L A L Y  
 CTAAGTCAAT TTGATTTTGA AGGTCCTGCT CGTGCTTTCT TAGATGTTAC AGCCAACATT 180  
 L S Q F D F E G P A R A F L D V T A N I  
 ATTCACGAAG ACTTCTCAGG TGAAAACTT GGAGTAGCTT ATGAAGATGA CTGTATGGGA 240  
 I H E D F S G E K L G V A Y E D D C M G  
 CCATTGAGCA TGAATGCAGG TGTCTTCAG TTTGATGAAA CTAATGATGA TAATACTATC 300  
 P L S M N A G V F Q F D E T N D D N T I  
 GCTCTTAATT TCCGTTACCC ACAAGGGACA GATGCTAAAA CTATCCAAAC TAAGCTTGAG 360  
 A L N F R Y P Q G T D A K T I Q T .K L E  
 AAACCTAACG GAGTTGAAAA AGTGACTCTT TCTGACCATG AACACACACC AACTATGTA 420  
 K L N G V E K V T L S D H E H T P H Y V  
 CCTATGGACG ATGAATTAGT ATCAACCTTA CTAGCTGTCT ATGAAAAGCA AACTGGTCTT 480  
 P M D D E L V S T L L A V Y E K Q T G L  
 AAAGGACATG AACAGGTTAT TGGTGGTGGG ACATTTGGTC GCTTACTTGA ACGGGGTGTT 540  
 K G H E Q V I G G G T F G R L L E R G V  
 GCATACGGTG CCATGTTCCC AGGAGATGAA AACACTATGC ATCAAGCTAA TGAGTACATG 600  
 A Y G A M F P G D E N T M H Q A N E Y M  
 CCTTTAGAAA ATATTTTCCG TTCGGCTGCT ATCTACGCAG AAGCTATCTA TGAATTAATC 660

P L E N I F R S A A I Y A E A I Y E L I  
 AAATAAAATA ATCCTTAAAC TAAATATGTG ATCAATGATA AAGGGTGGTG AAGACATGAA 720  
 K .  
 AGTGTCTTTG CCTCTTTTCA TAAGGTTAGA TTTGGAGACT TTATGACTGA CTTGGAAAAA 780  
 M T D L E K  
 |---->  
 ATTATTAAAG CAATAAAAAG TGATTCACAG AATCAAAATT ATACAGAAAA TGGTATTGAT 840  
 I I K A I K S D S Q N Q N Y T E N G I D  
 CCTTTGTTTG CTGCTCCTAA AACAGCTAGG ATCAATATTG TTGGCCAAGC ACCTGGTTTA 900  
 P L F A A P K T A R I N I V G Q A P G L  
 AAAACTCAAG AAGCAAGACT CTATTGGAAA GATAAATCTG GAGATCGTCT ACGCCAGTGG 960  
 K T Q E A R L Y W K D K S G D R L R Q W  
 CTTGGAGTTG ATGAAGAGAC ATTTTACCAT TCTGGAAAAAT TTGCTGTTTT ACCTTTAGAT 1020  
 L G V D E E T F Y H S G K F A V L P L D  
 TTTTATTACC CAGGCAAAGG AAAATCAGGA GATTTACCCC CTAGAAAAGG TTTTGC GGAG 1080  
 F Y Y P G K G K S G D L P P R K G F A E  
 AAATGGCACC CTCTTATTTT AAAAGAAATG CCTAATGTTC AATTGACCTT GCTAGTTGGT 1140  
 K W H P L I L K E M P N V Q L T L L V G  
 CAGTATGCTC AGAAATATTA TCTTGAAGC TCCGCACATA AAAATCTAAC AGAAACAGTT 1200  
 Q Y A Q K Y Y L G S S A H K N L T E T V  
 AAAGCTTACA AAGACTATCT ACCCGATTAT TTACCCCTGG TTCACCCATC ACCGCGAAAT 1260  
 K A Y K D Y L P D Y L P L V H P S P R N  
 CAAATTTGGC TAAAGAAGAA TCCATGGTTT GAAAAAGATC TAATCGTTGA TTTACAAAAG 1320  
 Q I W L K K N P W F E K D L I V D L Q K  
 ATAGTAGCAG ATATTTTAAA AGATTAAGGA TAGGAGTTGG TATGAGAGAT AATCATCTAC 1380  
 I V A D I L K D .  
 M R D N H L H  
 |---->  
 ACACGTATTT TTCCTATGAT TGTCAAACGG CATTGAGGA CTATATTAAT GGTTTTACAG 1440  
 T Y F S Y D C Q T A F E D Y I N G F T G  
 GTGAATTTAT CACGACAGAA CATTTTGATT TATCAAATCC TTACACCGGT CAAGACGATG 1500  
 E F I T T E H F D L S N P Y T G Q D D V  
 TTCCTGATTA TAGTGCTTAT TGTCAAAAA TAGATTATCT TAATCAGAAA TATGGAAATC 1560  
 P D Y S A Y C Q K I D Y L N Q K Y G N R  
 GATTTAAAAA AGGAATTGAA ATCGGTTATT TTAAAGATAG GGAATCAGAT ATTTTAGATT 1620  
 F K K G I E I G Y F K D R E S D I L D Y  
 ATTTAAAAA TAAAGAATTT GATTTAAAAC TATTGTCAAT CCATCATAAT GGTAGGTATG 1680  
 L K N K E F D L K L L S I H H N G R Y D  
 ATTATCTGCA AGAAGAAGCT CTGAAAGTAC CAACAAAGGG AGCTTTTAGC AGATTACTTT 1740  
 Y L Q E E A L K V P T K G A F S R L L .  
 AATCGTATGG AATTTGCCAT AGGCCGTGTG GAAGCGCACG TTTTAGCTCA CTTTGATTAT 1800  
 GGTTTTCGTA AGTTAACTT AGATGTAGAA GATTTAAAAC CGTTTGAAAC GCAATTGAAG 1860  
 CGCATTTTCA TAAAGATGTT ATCTAAGGGG TTAGCTTTTG AACTAAATAC CAAATCCCTT 1920



22/40

AAAACTAACG CCAAAGAGAT TGGTTTTCTA ATCTTAGATG AAAGTAAGAC AGGAGATGCA 3300  
 K T N A K E I G F L I L D E S K T G D A  
 GTGAAAGTTC AACCCAACGA CTATGTTTTT AGAGATTTAG CTAACCATAA CCAAATTTTT 3360  
 V K V Q P N D Y V F R D L A N H N Q I F  
 GTAAAAGATA AGGATCCAAA GGTTTATAAT AATCCTTATT ACATTGATCA AGTGCAGCTA 3420  
 V K D K D P K V Y N N P Y Y I D Q V Q L  
 AAGGATGCCC AACAAATTGA TTTAACAAGT ATTCAAGCAA GTTTTACAAC TCTAGATGGG 3480  
 K D A Q Q I D L T S I Q A S F T T L D G  
 GTAGATAAAA CTGAAATTTT AAAAGAATTG AAAGTGACTG ATAAAAATCA AAATGCTATA 3540  
 V D K T E I L K E L K V T D K N Q N A I  
 CAAATTTCTG ATATCACTCT CGATACTAGT AAATCTCTTT TAATAATCAA AGGCGACTTT 3600  
 Q I S D I T L D T S K S L L I I K G D F  
 AATCCTAAAC AAGGTCATTT CAACATATCT TATAATGGTA ACAATGTCAT GACAAGGCAA 3660  
 N P K Q G H F N I S Y N G N N V M T R Q  
 TCTTGGGAAT TTAAAGACCA ACTTTATGCT TATAGTGGA ATTTAGGTGC AGTTCTCAAT 3720  
 S W E F K D Q L Y A Y S G N L G A V L N  
 CAAGATGGTT CAAAAGTTGA AGCCAGCCTC TGGTCACCGA GTGCTGATAG TGTCACTATG 3780  
 Q D G S K V E A S L W S P S A D S V T M  
 ATTATTTATG ACAAAGATAA CCAAAACAGG GTTGTAGCGA CTACCCCCCT TGTGAAAAAT 3840  
 I I Y D K D N Q N R V V A T T P L V K N  
 AATAAGGTG TTTGGCAGAC GATACTTGAT ACTAAATTAG GTATTAAAA CTATACTGGT 3900  
 N K G V W Q T I L D T K L G I K N Y T G  
 TACTATTATC TTTACGAAAT AAAAAGAGGT AAGGATAAGG TTAAGATTTT AGATCCTTAT 3960  
 Y Y Y L Y E I K R G K D K V K I L D P Y  
 GCAAAGTCAT TAGCAGAGTG GGATAGTAAT ACTGTTAATG ATGATATTAA AACGGCTAAA 4020  
 A K S L A E W D S N T V N D D I K T A K  
 GCAGCTTTTG TAAATCCAAG TCAACTTGA CCTCAAAATT TAAGTTTTGC TAAAATTGCT 4080  
 A A F V N P S Q L G P Q N L S F A K I A  
 AATTTTAAAG GAAGACAAGA TGCTGTTATA TACGAAGCAC ATGTAAGAGA CTTCACTTCT 4140  
 N F K G R Q D A V I Y E A H V R D F T S  
 GATCGATCTT TGGATGGAAT ATTAATAAAT CAATTTGGTA CCTTTGCAGC CTTTTCAGAG 4200  
 D R S L D G K L K N Q F G T F A A F S E  
 AAAC TAGATT ATTTACAGAA ATTAGGAGTT ACACACATTC AGCTTTTACC GGTATTGAGT 4260  
 K L D Y L Q K L G V T H I Q L L P V L S  
 TATTTTTATG TTAATGAAAT GGATAAGTCA CGCTCAACAG CTTACACTTC CTCAGACAAT 4320  
 Y F Y V N E M D K S R S T A Y T S S D N  
 AATTACAATT GGGGCTATGA CCCACAGAGC TATTTTGCTC TTTCTGGGAT GTATTGAGG 4380  
 N Y N W G Y D P Q S Y F A L S G M Y S E  
 AAACCAAAAG ATCCATCAGC ACGTATCGCC GAATTAAAAC AATTAATACA TGATATTCAT 4440  
 K P K D P S A R I A E L K Q L I H D I H

AAACGTGGCA TGGGGGTTAT ACTTGATGTC GTCTATAATC ACACTGCAAA AACTTATCTC 4500  
 K R G M G V I L D V V Y N H T A K T Y L  
 TTTGAGGATA TAGAACCTAA TTATTATCAC TTTATGAATG AAGATGGTTC ACCAAGAGAA 4560  
 F E D I E P N Y Y H F M N E D G S P R E  
 AGTTTTGGAG GGGGACGTTT AGGAACCACT CATGCAATGA GTCGTCGTGT TTTGGTTGAT 4620  
 S F G G G R L G T T H A M S R R V L V D  
 TCCATTAAAT ATCTTACAAG TGAATTTAAA GTTGATGGTT TCCGTTTGA TATGATGGGA 4680  
 S I K Y L T S E F K V D G F R F D M M G  
 GATCATGATG CGGCTGCGAT TGAATTAGCT TATAAAGAAG CTAAAGCTAT TAATCCTAAT 4740  
 D H D A A A I E L A Y K E A K A I N P N  
 ATGATTATGA TTGGTGAGGG CTGGAGAACA TTCCAAGGCG ATCAAGGTCA GCCGGTTAAA 4800  
 M I M I G E G W R T F Q G D Q G Q P V K  
 CCAGCTGACC AAGATTGGAT GAAGTCAACC GATACAGTTG GCGTCTTTTC AGATGATATT 4860  
 P A D Q D W M K S T D T V G V F S D D I  
 CGTAATAGCT TGAAATCTGG TTTTCCAAAT GAAGGTACTC CAGCTTTCAT CACAGGTGGC 4920  
 R N S L K S G F P N E G T P A F I T G G  
 CCACAATCTT TACAAGGTAT TTTTAAAAAT ATCAAAGCAC AACCTGGGAA TTTTGAAGCA 4980  
 P Q S L Q G I F K N I K A Q P G N F E A  
 GATTGCCAG GAGATGTGGT GCAGTATATT GCTGCACATG ATAACCTTAC CTTGCATGAT 5040  
 D S P G D V V Q Y I A A H D N L T L H D  
 GTGATTGCAA AATCAATT (SEQ ID NO:22) 5058  
 V I A K S I .

FIG. 4a

NLKAELSVED EQYTATVYGK SAHGSTPQEG VNGATYLALY LSQFDFEGPA 50  
 RAFLDVTANI IHEDFSGEKL GVAYEDDCMG PLSMNAGVFQ FDETNDNTI 100  
 ALNFRYPQGT DAKTIQTKLE KLNGVEKVTL SDHEHTPHYV PMDDELVSTL 150  
 LAVYEKQTGL KGHEQVIGGG TFGRLLEGRV AYGAMFPGDE NTMHQANEYM 200  
 PLENIFRSAA IYAEAIYELI K (SEQ ID NO:23) 221

FIG. 4b

MTDLEKIIKA IKSDSQNQNY TENGIDPLFA APKTARINIV GQAPGLKTQE 50  
 ARLYWKDKSG DRLRQWLGV D EETFYHSGKF AVLPLDFYYP GKGKSGDLPP 100  
 RKGFAEKWHP LILKEMPNVQ LTLVLGQYQA KYLLGSSAHK NLTETVKAYK 150  
 DYLPDYLPLV HPSPRNQIWL KKNPWFEKDL IVDLQKIVAD ILKD 194  
 (SEQ ID NO:24)

FIG. 4c

MRDNLHHTYF SYDCQTAFED YINGFTGEFI TTEHFDLSNP YTGQDDVPDY 50  
SAYCQKIDYL NQKYGNRFKK GIEIGYFKDR ESDILDYLN KEFDLKLISI 100  
HHNGRYDYLO EEALKVPTKG AFSRLL (SEQ ID NO:25) 126

FIG. 4d

MKRKDLFGDK QTQYTIRKLS VGVASVTTGV CIFLHSPQVF AEEVSVSPAT 50  
TAIAESNINQ VDNQQSTNLK DDINSNSETV VTPSDMPDTK QLVSDETDTQ 100  
KGVTEPDKAT SLLEENKGPV SDKNTLDLKV APSTLQNTPD KTSQAIGAPS 150  
PTLKVANQAP RIENGYFRLH LKELPQGHVP ESTGLWIWGD VDQPSSNWPV 200  
GAIPMTDAKK DDYGYVDFK LSEKQRKQIS FLINNKAAGT NLSGDHHPILL 250  
RPEMNQVWID EKYGIHTYQP LKEGYVRIN YLSSSSNYDHL SAWLFKDVAT 300  
PSTTWPDGSN FVNQGLYGRY IDVSLKTNK EIGFLILDES KTGDAVKVQP 350  
NDYVFRDLAN HNQIFVKDKD PKVYNNPYYI DQVQLKDAQQ IDLTSIQASF 400  
TTLDGVDKTE ILKELKVTDK NQNAIQISDI TLDTSKSLLI IKGDFNPKQG 450  
HFNISYNGNN VMTRQSWEFK DQLYAYSGNL GAVLNQDGSK VEASLWSPSA 500  
DSVTMIIYDK DNQNRVVATT PLVKNNKGVW QTILDTKLGI KNYTGYYLY 550  
EIKRGKDKVK ILDPYAKSLA EWDSNTVNDD IKTAKAAAFVN PSQLGPNLS 600  
FAKIANFKGR QDAVIYEAHV RDFTSDRSLD GKLKNQFGTF AAFSEKLDYL 650  
QKLGVTHIQL LPVLSYFYVN EMDKSRSTAY TSSDNNYNWG YDPQSYFALS 700  
GMYSEKPKDP SARIAELKQL IHDIHKGGMG VILDVVYNHT AKTYLFEDIE 750  
PNYYHFMNED GSPRESFGGG RLGTTHAMSR RVLVDSIKYL TSEFKVDGFR 800  
FDMMGDHDA AIELAYKEAK AINPNMIMIG EGWRTFQGDQ GQPVKPADQD 850  
WMKSTDVTGV FSDDIRNSLK SGFPNEGTPA FITGGPQSLQ GIFKNIKAQP 900  
GNFEADSPGD VVQYIAAHN LTLHDVIAKS I (SEQ ID NO:26) 931

FIG. 4e

AATTCAAAGT TTGACAGAAG GTCAACTTCG TTCTGATATC CCTGAGTTCC GTGCTGGTGA 60  
 I Q S L T E G Q L R S D I P E F R A G D  
 ---->  
 TACTGTACGT GTTCACGCTA AAGTTGTTGA AGGTACTCGC GAACGTATTC AGATCTTTGA 120  
 T V R V H A K V V E G T R E R I Q I F E  
 AGGTGTTGTT ATCTCACGTA AAGGTCAAGG AATCTCAGAA ATGTACACAG TACGTAAAT 180  
 G V V I S R K G Q G I S E M Y T V R K I  
 TTCTGGTGGT ATCGGTGTAG AGCGTACATT CCCAATTCAC ACTCCTCGTG TTGATAAAAT 240  
 S G G I G V E R T F P I H T P R V D K I  
 CGAAGTTGTT CGTTATGGTA AAGTACGTCG TGCTAAACTT TACTACTTAC GCGCATTGCA 300  
 E V V R Y G K V R R A K L Y Y L R A L Q  
 AGGTAAAGCT GCACGTATTA AAGAAATCCG TCGTTAATTT TGATGATCAG ATTTTAAAAA 360  
 TGCTTGTTG TTTGAGGATA GTAACATATGT TTTAAACTG GACAACCAAG ACGTAAAAA 420  
 TCTGCCTGTG GGCAGTTTTT TTACTAGGTC CCCTTAGTTC AATGGATATA ACAACTCCCT 480  
 . H I Y C S G  
 CCTAAGGAGT AATTGCTGGT TCGATTCCGG CAGGGGACAT ATTCATTGCA TGTAATAGC 540  
 G L S Y N S T R N R C P V Y E N C T F L  
 GGTTTAGAGC TATTTTGCCC CAAATTTCTC TGATTAAGTT TATCGTTCCT ATCTTTTTGT 600  
 P K S S N Q G L N R Q N L K D N R D K Q  
 TCTTGTAATT GATGTGCGTA AACTTCTAAA GTGATATTTA AATTCTCGTG ATCTAAACT 660  
 E Q L Q H A Y V E L T I N L N E H D L V  
 TGAGAGATGG AAATTAGATA GCTTGCAAAT GTATGCCTGA GAGAGTGCAC TCGTACCTCG 720  
 Q S I S I L Y S A F T H R L S H V R V E  
 CGACCAGTTA TTTTTCGGAT AGTTTTATTG ACTGCATTAT TTGAAAGTTT GTCGAATAAT 780  
 R G T I K R I T K N V A N N S L K D F L  
 CTGTCGTTTT TATTTTTTGT AAATTCATGC AAAAAAATA ATGTATCATT GTCAATTGGT 840  
 R D N K N K T F E H L F F L T D N D I P  
 ATATTTCTGA TACTACTTTT GTTTTTTGT GGCAGGTATC TTTGGTTGAA ATGATAATCC 900  
 I N R I S S K N K T P L Y R Q N F H Y D  
 CAAGTTTTAT TAATTGATAA ATATTTGTTA GTGTAATCAA TATCATTAAC TGTAAACCT 960  
 W T K N I S L Y K N T Y D I D N V T L G  
 AAACATTCAG CGAAGCGCAT GCCAGTTTTA GCGATGAGGT ATAACGCTGC ATACGATTGA 1020  
 L C E A F R M  
 <----|  
 TGTTGTGATT TTTCTTTACA AATTTTTATC AAGCGTAAGT ATTCATTGGT TTCAAGAAAT 1080  
 TTTATCTCTA TTTACGCCCC TTATTTTTTG CTTTAACCTT AGTGAATAAA CAAAAATTTT 1140  
 TTTCTATATA TCCCTCGTGA ACAGCCATGG ATACGCAGGC TTTTACATGT ATGTTAAAAC 1200  
 GCTTTACTGT ATCTTGCACA TGCGTTTGAC TATAATGATT TATGACTTGT TGATATTTAG 1260

TGGAAGTAAT ATTGCAAAGT AATATATTTT CTATTATATG TTTATACGAT ATTCGATATT 1320  
CCCCCCGTT GTCGCGTTTA CGGAAATACG CCATTGATAT ACTCCACATT AGCTAAAGAA 1380  
CAGGGTGTTT AAGGCTACCT TGATGGAAAA GGCTCTCTTA GAGATATTTG TAAATGGTAT 1440  
GATATCTCAA GTCGCTCTGT TCTCCAAAAG TGGATAAAAC GGTATACTAG TGGTGAAGAC 1500  
TTGAAAGCCA CTAGTAGAGG ATATAGCCGT ATGAAACAAG GAAGGCAAGC CACATTTGAA 1560  
GAACGTGTAG AGATTGTTAA CTACACCATT GCCCATGGGA AAGACTATCA AGCAGCTATT 1620  
GAGAAGTTTG GTGTTTCCTA CCAACAAATT TATTCTTGGG TGCCTAAGCT TGAGAAGAAT 1680  
GGCTCACAAG GTTTGGTTGA TAGACGTGTG AAAGGGTTGG AGAGTAGGCC TGATTTAACC 1740  
GAGATTGAGC AACTTTAACT CAAGATTAAC CAATTGGAGG AACGTAATCG TCTCTTAGAA 1800  
ATCGAGGTTA GTTTACTAAA AAAGTTAGAA GACATCAAAC GAGGAAACAG ACGGTAAGAC 1860  
TAGGTAAGCA TTTAGCGGAG TTCCAAGTAA TCAAGAATTA TTACGATGAG GAATCTAATG 1920  
TGCCTATTCA GGCCTTATGC CAACTCTTGA AGGGGTCTCG TTCAGGCTAT TACAAGTGGC 1980  
TCAATCGTCA AAAACAGAT TTTGAGACAA AAAATACAAA GCTAATGGCT AAAATCAAGG 2040  
AACTTCGTAG ACTCTACAAT GGTATCTTAG GTTATCGCCG TATGACAACA TTTATTAATC 2100  
GTCAACTTGG GACAACCTAA AACAAGAAAC GGATTCGTTG ATTGATGAAC ATTCTGGGGA 2160  
TTAGTTCAGT CATTCGTCGT GTTAGCCATG CTTGTACAAA AGCTGGTGAC AGATTTTACG 2220  
AAGAAAATAT TCTTAATCGT GAATTTACAG CCACAGCTCA TAACCAGAAA TGGTGCACAG 2280  
ATGTCACCTA TCTTCAATAC GGTCTGGGAG CTAAAGCTTA TCTCAGTGCG ATTAAAGACC 2340  
TGTATAACGG TTCTATTATC GCTTATGAGA TTAGTCACAA CAATGAAATC CACTTGTTAT 2400  
GAAGACCATT AAAAAGGGGC TAGAGCTCAA TCCAGGAGCC ACACCTATCA TCCATAGCGA 2460  
TTGAGGTAGT CAATATACTT CCAAAGAATA CCGTTATATC ATACAACAAG CTGGTCTGAC 2520  
CTTATCCATG TCCCGGATTG GCAAATGTAT TGATAATGCA CCAACTGAAA GTTTCTTTGG 2580  
GTTTTTCAAG ACTGAGTCTT ACCACCTTAA GAAATACAAC TCTTATGATG AGTTGGTCAA 2640  
TGATGTGGCA CGTTATATCG AATTCTACAA CACACAACGT TATCAATCAA AATTAAACAA 2700  
CCTGACTCCT CTAGAATTCA GGAATCAGGT TGCATAACTT ATCTTTTATT ATTTGACTGT 2760  
CTACTTGACA GGGAGCCGTT CAGATTGCTT AACCTTTCTA AATTTGCTAA AATAGCTACA 2820  
AGAAAACGAG CCATTTAATG CTTATTTCTT ATACTGTCTT GCCTCACGCT CTCCTCGACC 2880  
AAAAATTGAG CGTGAGGCTT TTTGTTTCAT TAAACGATGA TATTTCCATA TTCATCAGTT 2940  
TGTTTTCCGA GAGCCATCAA AGCTTCGATA AGGTCGATAA TTCCAGGAAT AAAGGTAATA 3000  
CTAAAAATAA TATATAAAAA AACCTGGCCT ATTTTTCCTG CGTAAAATTT ATGCGCTCCA 3060  
ATGCCGCCCA AAAGAACGTT AATAAAACAT AAATACTAT GTTAGCATAA GACTTTATTT 3120

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A L N K   L K D   F K I   D K S K   Y S I   K K D
AATAAGCAT TCGAAGAGTC TTTAGAGTCA GTGAGTGGAA TAAAACATAT AATTAAAATA 4680
N K A F   E E S   L E S   V S G I   K H I   I K I
ATGACTTATT CGATTATGTT AGGTGGAATA GTTGTCTTTT CATTAACTTT GATTCTATGG 4740
M T Y S   I M L   G G I   V V L S   L I L   I L W
TTAAGAGAAA GAATTTATGA AATAGGTATA TTTTATCTA TTGGAACAAC TAAGATACAA 4800
L R E R   I Y E   I G I   F L S I   G T T   K I Q
ATTATAAGGC AATTTATATT TGAGTTAATA TTCATATCAA TACCAAGTAT AATATCCTCC 4860
I I R Q   F I F   E L I   F I S I   P S I   I S S
TTATTTTTAG GGAATCTACT ATTAAGAATA ATTGTAGAAG GATTTATTAA CTCAGAGAAC 4920
L F L G   N L L   L K V   I V E G   F I N   S E N
TCAATGATTT TCGGTGGAAG TTTAATAAAT AAAAGCAGTT TTATGTTAAA CATAACAACA 4980
S M I F   G G S   L I N   K S S F   M L N   I T T
CTTGCGAGAAA GTTATTTAAT ATTAATAAGT ATTATTGTTT TATCAGTTGT AATGGCCTCT 5040
L A E S   Y L I   L I S   I I V L   S V V   M A S
TCATTAATAT TATTTAAGAA ACCACAAGAA ATATTATCAA AAATAAGTTA GGAGCAAATA 5100
S L I L   F K K   P Q E   I L S K   I S .
ATGGATATAT TAGAAATAAA GAATGTAAAT TACAGTTACG CAAATTCTAA AGAAAAAGTT 5160
M D I L   E I K   N V N   Y S Y A   N S K   E K V
|---->
TTGTCAGGAG TAAATCAAAA ATTTGAACTT GGAAAGTTTT ATGCGATAGT AGGGAAGTCA 5220
L S G V   N Q K   F E L   G K F Y   A I V   G K S
GGAACAGGAA AATCCACACT TCTTTCCTTA CTTGCGAGGAC TTGATAAAGT TCAAACAGGA 5280
G T G K   S T L   L S L   L A G L   D K V   Q T G
AAAATCTTGT TTAAGAATGA AGATATAGAA AAGAAAGGAT ATAGTAATCA CAGAAAAAAT 5340
K I L F   K N E   D I E   K K G Y   S N H   R K N
AATATATCTT TGGTATTTCA AAATTATAAT TTAATAGATT ATTTATCGCC GATTGAAAAT 5400
N I S L   V F Q   N Y N   L I D Y   L S P   I E N
ATTAGACTAG TAAATAAATC AGTAGATGAG AGTATCTTGT TCGAATTAGG TTTAGATAAA 5460
I R L V   N K S   V D E   S I L F   E L G   L D K
AAACAAATAA AAAGAAATGT TATGAAATTA TCTGGTGGTC AGCAACAAAG GGTAGCTATT 5520
K Q I K   R N V   M K L   S G G Q   Q Q R   V A I
GCTAGGGCAC TGGTATCAGA TGCCCCAATA ATACTAGCTG ATGAGCCTAC CGGTAACCTA 5580
A R A L   V S D   A P I   I L A D   E P T   G N L
GACAGTGTTA CTGCTGGAGA AATAATT (SEQ ID NO:27) 5607
D S V T   A G E   I I .

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FIG. 5a



IQSLTEGQLR	SDIPEFRAGD	TVRVHAKVVE	GTRERIQIFE	GVVISRKGQG	50
ISEMYTVRKI	SGGIGVERTF	PIHTPRVDKI	EVVRYGKVRR	AKLYYLRALQ	100
GKAARIKEIR	R	(SEQ ID NO:28)			111

FIG. 5b

MRFAECLGLT	VNDIDYTNKY	LSINKTWDYH	FNQRYLPTKN	KSSIRNIPID	50
NDTLFFLHEF	TKNKNDRLED	KLSNNAVNKT	IRKITGREVR	VHSLRHTFAS	100
YLISISQVLD	HENLNITLEV	YAHQLQEQKD	RNDKLNQORN	GQNSSKPLET	150
CNEYVPCNRN	TSNYSLGGSC	YIH	(SEQ ID NO:29)		173

FIG. 5c

MKSSNEIEKA	LYESSNSSIS	ITKKDGKYFN	INQFKNIEKI	KEVEEKIFQY	50
DGLAKLKDLD	VVSGEQSINR	EDLSDEFKNV	VSLEATSNTK	RNLLFSSGVF	100
SFKEGKNIEE	NDKNSILVHE	EFAKQNKLLK	GDEIDLELLD	TEKSGKIKSH	150
KFKIIGIFSG	KKQETYTGSL	SDFSENMVFF	DYSTSQEILN	KSENNRIANK	200
ILMYSGSLES	TELALNKLKD	FKIDKSKYSI	KKDNKAFEEES	LESVSGIKHI	250
IKIMTYSIML	GGIVVLSLIL	ILWLRERIYE	IGIFLSIGTT	KIQIIRQFIF	300
ELIFISIPSI	ISSLFLGNLL	LKVIVEGFIN	SENSMIFGGS	LINKSSFMLN	350
ITTLAESYLI	LISIIVLSVV	MASSLILFKK	PQEILSKIS		389
(SEQ ID NO:30)					

FIG. 5d

MDILEIKNVN	YSYANSKEKV	LSGVNQKFEL	GKFYAIVGKS	GTGKSTLLSL	50
LAGLDKVQTG	KILFKNEDIE	KKGYSNHRKN	NISLVFQNYN	LIDYLSPIEN	100
IRLVNKSVD	SILFELGLDK	KQIKRNVMKL	SGGQQQRVAI	ARALVSDAPI	150
ILADEPTGNL	DSVTAGEII	(SEQ ID NO:31)			169

FIG. 5e

CATATGACAA	TATTTTTC	AGTCTACATC	ACTTACTCGC	CTGTCGTGGA	AAATCTGGCA	60
ATACATTAAT	CGACCAATTA	GTTGCTGATG	GTTTACTTCA	TGCAGATAAT	CACTACCATT	120
TTTTCAATGG	GAAGTCTCTG	GCCACTTTCA	ATACTAACCA	ATTGATTTCG	GAAGTTGTCT	180
ATGTTGAAAT	ATCCTTAGAT	ACTATGTCTA	GTGGTGAACA	TGATTTAGTA	AAAGTTAACA	240
TTATCAGACC	CACTACCGAG	CATACTATCC	CCACGATGAT	GACAGCTAGC	CCCTATCATC	300
AAGGTATCAA	TGATCCTGCC	GCAGACCAAA	AAACATACCA	AATGGAGGGT	GCGCTAGCAG	360
TTAAACAGCC	TAAACACATA	CAAGTTGACA	CAAAACCATT	TAAAGAAGAA	GTAAAACATC	420
CTTCAAAATT	ACCCATCAGC	CCTGCAACTG	AAAGCTTCAC	ACACATTGAC	AGTTATAGTC	480
TCAATGACTA	TTTTCTTTCT	CGTGGTTTTG	CTAATATATA	CGTTTCAGGT	GTGGGTACTG	540
CTGGCTCTAC	GGGTTTCATG	ACCAGTGGGG	ATTACCAACA	AATACAAAGC	TTTAAAGCAG	600
TCATTGATTG	GTTAAATGGT	AAGGTTACTG	CATTACACAAG	TCATAAACGA	GATAAACAAAG	660
TCAAGGCTGA	TTGGTCAAAC	GGCCTTG TAG	CAACCACAGG	TAAATCTTAT	CTCGGTACCA	720
TGTCAACTGG	TTTAGCAACA	ACTGGCGTTG	AGGGGCTGAA	AGTCATTATC	GCTGAAGCCG	780
CAATCTCCAC	ATGGTATGAT	TATTATCGAG	AAAATGGGCT	TGTGTGTAGT	CCAGGCGGCT	840
ACCCCGGTGA	AGATTTAGAC	GTTTTAACAG	AATTAACATA	CTCACGAAAC	CTCTTAGCTG	900
GTGATTACAT	CAAAAACAAC	GATTGCTATC	AAGCATTGTT	AAATGAACAA	TCAAAAAGCAA	960
TTGACCGTCA	AAGTGGGGAT	TACAACCAAT	ACTGGCATGA	CCGTAATTAC	CTAACTCAGC	1020
TCAATAATGT	CAAAAGTCGA	G TAGTTTACA	CTCATGGACT	ACAGGATTGG	AATGTTAAGC	1080
CAAGACATGT	CTACAAAGTT	TTCAATGCAT	TGCCTCAAAC	CATCAAAAAA	CACCTTTTTT	1140
TACATCAAGG	TCAACATGTG	TATATGCATA	ATTGGCAGTC	GATTGATTTT	CGTGAAAGCA	1200
TGAATGCCTT	ACTAAGCCAA	GAAGTACTTG	GCATTGACAA	TCATTTCCAA	TTAGAAGAGG	1260
TCATTTGGCA	AGATAATACT	ACTGAGCAAA	CTTGGCAAGT	TTTAGATGCT	TTCGGAGGAA	1320
ACCATCAAGA	GCAAATTGGT	TTAGGTGATA	GTAAAAAACT	TATTGATAAC	CATTATGACA	1380
AAGAAGCCTT	TGATACTTAT	TGTAAAGACT	TCAATGTGTT	CAAAAATGAT	CTTTTCAAGG	1440
GAAATAATAA	AACCAATCAA	ATCACTATTA	ATCTTCCTCT	AAAGAAAAAT	TATCTCCTGA	1500
ATGGACAGTG	CAAACTCCAT	CTACGTGTTA	AAACTAGTGA	CAAAAAGGCC	ATTTTATCAG	1560
CCCAAATCTT	AGACTATGGT	CCTAAAAAAC	GATTCAAAGA	TACACCAACC	ATCAAATTCT	1620
TAAACAGCCT	TGATAATGGT	AAAAATTTTG	CCAGAGAAGC	TTTACGTGAA	CTCCCGTTTA	1680
CTAAAGATCA	TTATCGTGTC	ATCAGTAAAG	GTGTCTTGAA	CCTTCAAAAT	CGTACAGACT	1740
TACTTACAAT	TGAGGCTATC	GAGCCAGAAC	AATGGTTTGA	TATCGAGTTT	AGCCTCCAAC	1800
CAAGTATATA	TCAATTGAGT	AAAGGTGATA	ATCTAAGGAT	TATCCTTTAT	ACAAGTATT	1860
TTGAACATAC	CATTGAGAT	AATGCTAGTT	ACTCTATAAC	AGTAGATTTG	AGTCAATCTT	1920
ATTTAACTAT	CCCAACTAAT	CAAGGAAATT	AACTTATGAA	ACTTCTTACT	AAAGAACGGT	1980
TTGATGATTC	TCAACACTTT	TGGTACCAGA	TCAATTTATT	ACAAGAGAGT	AACTTCGGAG	2040
CAGTTTTTGA	CCATGATAAT	AAAAACATTC	CACAGGTTGT	TGCAACTATT	GTTGATGATT	2100
TACAAGGTTT	CGGAAGTTTC	AATCATTCTT	GGTATTTTGG	CAATACTACT	GATACTTCCA	2160
TCCTTATGAT	TGCTCATTTA	AATCGAAAAT	TCTATATTCA	GGTTAATTTA	AAGGACTTTG	2220
ACTTTGCACT	CAATTTAATA	GCTATAAATA	ATTGGAAGAG	TCTCCTCCAA	ACTCAACTTG	2280
AAGCTCTAAA	CGATACCCTA	GCAATATTTT	AATAAATAAG	G TAGAATGGA	GTGACAAAGC	2340
AACGCGAGGG	AGACTGATTA	ATGTCATCTT	ATTGGAATAA	CTATCCTGAA	CTTAAAAAAA	2400

ATATTGATGA	AACCAATCAA	CTAATTCAAG	AAAGAATACA	GGTCAGAAAT	AAAGATATTG	2460
AAGCGGCGCT	AAGCCAACTC	ACAGCTGCGG	GAGGAAAACA	GCTCAGACCA	GCATTCTTTT	2520
ACCTTTTTTC	TCAACTTGGT	AATAAGGAGA	ATCAAGATAC	TCAGCAACTA	AAGAAAATCG	2580
CTGCTTCTTT	AGAAATCCTT	CACGTTGCTA	CATTAATCCA	TGATGATGTC	ATTGATGACT	2640
CACCACTAAG	ACGTGGAAAT	ATGACCATTC	AAAGCAAGTT	TGGCAAAGAC	ATCGCAGTTT	2700
ATACTGGGGA	TTTACTTTTC	ACAGTCTTTT	TCGATCTTAT	TTTAGAATCT	ATGACTGATA	2760
CACCATTTAT	GAGGATTAAT	GCAAAAATCTA	TGCGTAAAT	TCTCATGGGA	GAATTGGACC	2820
AGATGCACCT	TCGTTACAAT	CAACAACAAG	GTATCCATCA	CTATTTACGT	GCGATTTTCAG	2880
GTAAGACAGC	CGAACTCTTT	AAATTAGCTA	GCAAAGAAGG	AGCTTACTTT	GGTGGTGCAG	2940
AGAAGGAGGT	TGTTCTGCTA	GCAGGCCATA	TCGGCTTTAA	CATTGGTATG	ACATTCCAAA	3000
TTTTGGATGA	TATCCTGGAT	TATACTGCAG	ATAAAAAAAC	ATTTAATAAG	CCTGTCTTAG	3060
AGGATTTAAC	ACAAGGCGTT	TACAGCCTTC	CTCTACTTCT	TGCCATTGAA	GAAAATCCTG	3120
ATATTTTCAA	ACCTATTTTA	GATAAAAAAA	CAGATATGGC	TACTGAAGAC	ATGGAAAAAA	3180
TTGCTTATCT	CGTCGTTTCC	CATAGAGGTG	TTGACAAAGC	TCGCCATCTA	GCTCGTAAAT	3240
TTACTGAGAA	AGCTATTAGT	GACATAAATA	AGCTACCCCA	GAACCTCTGCA	AAAAAACAGT	3300
TGCTACAATT	AACTAATTAC	CTTTTAAAAC	GCAAAATTTA	AATAATAAAA	AAACATTCCA	3360
CAATGCTAGA	AAAGCAGTTA	GGGAATGTTT	TTTTATTATC	ATTTATTTAT	CGCACCTATC	3420
AATCATCATA	GATCACCATC	ATCAGCGGCT	TTCAGCTGAC	GGTAACGTTG	ACTACTTTGA	3480
GACAATTCTT	GAGGAGAACC	TTCCAACCTC	AATTGCCCAT	TTTCTATAAA	TAAGATACGA	3540
TCAGCATGTT	CAATACCTTT	TAAGTGATGT	GTAATCCAAA	CTAAGGTCTT	ACCTTCCAAT	3600
TCTTTCATAA	ATACCCTTAG	TAAGGCTTGT	TCAGTAATAG	GATCAAGTCC	AACAGTTGGC	3660
TCATCTAAGA	TAACAATTGG	GACATCTTTT	AGTAAGATTG	TAGCCAAAGC	AATTCTATGC	3720
CTTTCGCCAC	CTGAAAACCT	AAGTCCAGCT	TCATCAACCA	TTGTATAGAG	ACCATCTGAT	3780
AAATCAGTGA	CCATCTCTTT	CAATCCAAC	CGTTCAAGAA	CTTTCCATAC	ATCTTCTTCA	3840
CTAGCATCTT	GGTTTCCAAT	GCGAATGTTA	TTTAGCAGGG	TTGTATTAAA	AAGGTAGGGC	3900
GCTTGTTGTA	TCACTCCAAT	ATAGTTAGAA	ATGCAATCAC	CAACTATTGA	AACATCAGCA	3960
CCGCCTAGGG	TAATCTTCCC	TTGACTTGCT	TTCAAGTCGC	CACGAAGTAG	ACTAGCTAAG	4020
GTACTCTTGC	CAGAACCACT	CCGCCCTAAA	ATAGCAATTT	TTTCTCCTTC	TTTAATATCC	4080
AAATCTAAAT	GATGCAAAAC	CCATTTCTCT	TGTGGCTTAT	ACTGGAAACT	TAAATTCTTG	4140
ACGGAAAAAT	CATATGGCTT	ATTAGGCAAT	T	(SEQ ID NO:32)		4171

FIG. 6a

YDNIFQSLHH	LLACRGKSGN	TLIDQLVADG	LLHADNHYHF	FNGKSLATFN	50
TNQLIREVVY	VEISLDTMSS	GEHDLVKVNI	IRPTTEHTIP	TMMTASPYHQ	100
GINDPAADQK	TYQMEGALAV	KQPKHIQVDT	KPFKEEVKHP	SKLPISPATE	150
SFTHIDSYSL	NDYFLSRGFA	NIYVSGVGTA	GSTGFMTSGD	YQQIQSEKAV	200
IDWLNGKVTA	FTSHKRDQV	KADWSNGLVA	TTGKSYLGTM	STGLATTGVE	250
GLKVIIAEEA	ISTWYDYYRE	NGLVCSPGGY	PGEDLDVLTE	LTYSRNLLAG	300
DYIKNNDCYQ	ALLNEQSKAI	DRQSGDYNQY	WHDRNYLTHV	NNVKSrvvYT	350
HGLQDWNVKP	RHVYKVFNAL	PQTIKKHLFL	HQGQHVYMHN	WQSIDFRESM	400
NALLSQELLG	IDNHFQLEEV	IWQDNTTEQT	WQVLDAFGGN	HQEQIGLGDS	450
KKLIDNHYDK	EAFDTCYCKDF	NVFKNDLFGK	NNKTNQITIN	LPLKKNYLLN	500
GQCKLHLRVK	TSDKKAILS	QILDYGPCKR	FKDTPTIKFL	NSLDNGKNFA	550
REALRELFT	KDHYRVISKG	VLNLQNRTDL	LTIEAIEPEQ	WFDIEFSLQP	600
SIYQLSKGDN	LRIILYTTDF	EHTIRDNASY	SITVDLSQSY	LTIPTNQGN	649

(SEQ ID NO:33)

FIG. 6b

MKLLTKERFD	DSQHFWYQIN	LLQESNFGAV	FDHDNKNIPQ	VVATIVDDLQ	50
GSGSSNHFWY	FGNTTDTISL	MIAHLNRKFY	IQVNLKDFDF	ALNLIAINNW	100
KSLLOTQLEA	LNDTLAIFQ	(SEQ ID NO:34)			119

FIG. 6c

MSSYWNNYPE	LKKNIDETNQ	LIQERIQVRN	KDIEAALSOL	TAAGGKQLRP	50
AFFYLFSQLG	NKENQDTQQL	KKIAASLEIL	HVATLIHDDV	IDDSPLRRGN	100
MTIQSKFGKD	IAVYTGDLLE	TVFFDLILES	MTDTPFMRIN	AKSMRKILMG	150
ELDQMHLRYN	QQQGIHHYLR	AISGKTAELE	KLASKEGAYF	GGAKEVVRL	200
AGHIGFNIGM	TFQILDDILD	YTADKKTFNK	PVLEDLTQGV	YSLPLLLAIE	250
ENPDIFKPIL	DKKTDATED	MEKIAYLVVS	HRGVDKARHL	ARKFTEKAIS	300
DINKLPQNSA	KKQLLQLTNY	LLKRKI	(SEQ ID NO:35)		326

FIG. 6d

LPNKPYDFSV KNLSFQYKPQ EKWVLHHLDL DIKEGEKIAI LGRSGSGKST 50  
LASLLRGDLK ASQGKITLGG ADVSIVGDCI SNYIGVIQQA PYLENTTLLN 100  
NIRIGNQDAS EEDVWKVLER VGLKEMVTDL SDGLYTMVDE AGLRFSGGER 150  
HRIALARILL KDVPIVILDE PTVGLDPITE QALLRVFMKE LEGKTLVWIT 200  
HHLKGIEHAD RILFIENGQL ELEGSPQELS QSSQRYRQLK AADDGDL 247  
(SEQ ID NO:36)

FIG. 6e

AATTCTATTT	GGAGGTTTTT	CTTGAATAAA	TGGTTAGTTA	AGGCAAGTTC	CTTAGTTGTT	60
TTAGGTGGTA	TGGTTTTATC	TGCGGGTTCC	CGAGTTTTAG	CGGATACTTA	TGTCCGTCCA	120
ATTGATAATG	GTAGAATTAC	AACAGGTTTC	AATGGTTATC	CTGGACATTG	TGGGGTGGAT	180
TATGCTGTTC	CGACTGGAAC	GATTATTAGG	GCAGTGGCAG	ATGGTACTGT	GAAATTTGCA	240
GGAGCTGGAG	CCAACTTTTC	TTGGATGACA	GACTTAGCAG	GAAATTGTGT	CATGATTCAA	300
CATGCGGATG	GAATGCATAG	TGGTTACGCT	CATATGTCAC	GTGTGGTGGC	TAGGACTGGG	360
GAAAAAGTCA	AACAAGGAGA	TATCATCGGT	TACGTAGGAG	CAACTGGTAT	GGCGACGGGA	420
CCTCACCTTC	ATTTTGAATT	TTTACCAGCT	AACCCTAATT	TTCAAAATGG	TTTCCATGGA	480
CGTATCAATC	CAACGTCACT	AATTGCTAAC	GTTGCGACCT	TTAGTGGA	AACGCAAGCA	540
TCAGCTCCAA	GCATTAAGCC	ATTACAATCA	GCTCCTGTAC	AGAATCAATC	TAGTAAATTA	600
AAAGTGATC	GAGTAGATGA	ATTACAAAAG	GTTAATGGTG	TTTGGTTAGT	CAAAAATAAC	660
ACCTAACGC	CGACTGGGTT	TGATTGGAAC	GATAATGGTA	TACCAGCATC	AGAAATTGAT	720
GAGGTTGATG	CTAATGGTAA	TTTGACAGCT	GACCAGGTTT	TTCAAAAAGG	TGGTTACTTT	780
ATCTTTAATC	CTAAAACTCT	TAAGACTGTA	GAAAAACCCA	TCCAAGGAAC	AGCTGGTTTA	840
ACTTGGGCTA	AGACACGCTT	TGCTAATGGT	AGTTCAGTTT	GGCTTCGCGT	TGACAACAGT	900
CAAGAACTGC	TTTACAAATA	GTTTGAGGTA	TTGATTCAAT	GTTTTAAATG	ACAGTTTTGT	960
TACTAACTAA	GTACAATTTT	TTTAAACCGT	CTGAAAATAA	TTTTTATAGT	CAGTAAAGTG	1020
TGATATTATA	GTCTCGGACT	AATAAAAAGG	AAATAGGAAT	TGAAGCAATG	AAAATGAATA	1080
AAAAGGTACT	ATTGACATCG	ACAATGGCAG	CTTCGCTATT	ATCAGTCGCA	AGTGTTCAAG	1140
CACAAGAAAC	AGATACGACG	TGGACAGCAC	GTACTGTTTC	AGAGGTAAAG	GCTGATTTGG	1200
TAAAGCAAGA	CAATAAATCA	TCATATACTG	TGAAATATGG	TGATACTACT	AGCGTTATTT	1260
CAGAAGCAAT	GTCAATTGAT	ATGAATGTCT	TAGCAAAAAT	TAATAACATT	GCAGATATCA	1320
ATCTTATTTA	TCCTGAGACA	ACACTGACAG	TAACCTACGA	TCAGAAGAGT	CATACTGCCA	1380
CTTCAATGAA	AATAGAAACA	CCAGCAACAA	ATGCTGCTGG	TCAAACAACA	GCTACTGTGG	1440
ATTTGAAAAC	CAATCAAGTT	TCTGTTGCAG	ACCAAAAAGT	TTCTCTCAAT	ACAATTTTCGG	1500
AAGGTATGAC	ACCAGAAGCA	GCAACAACGA	TTGTTTCGCC	AATGAAGACA	TATTCTTCTG	1560
CGCCAGCTTT	GAAATCAAAA	GAAGTATTAG	CACAAGAGCA	AGCTGTTAGT	CAAGCAGCAG	1620
CTAATGAACA	GGTATCAACA	GCTCCTGTGA	AGTCGATTAC	TTCAGAAGTT	CCAGCAGCTA	1680
AAGAGGAAGT	TAAACCAACT	CAGACGTCAG	TCAGTCAGTC	AACAACAGTA	TCACCAGCTT	1740
CTGTTGCCGC	TGAAACACCA	GCTCCAGTAG	CTAAAGTAGC	ACCGGTAAGA	ACTGTAGCAG	1800
CCCCTAGAGT	GGCAAGTGTT	AAAGTAGTCA	CTCCTAAAGT	AGAAACTGGT	GCATCACCAG	1860
AGCATGTATC	AGCTCCAGCA	GTTCTGTGA	CTACGACTTC	AACAGCTACA	GACAGTAAAGT	1920
TACAAGCGAC	TGAAGTTAAG	AGCGTTCGGG	TAGCACAAAA	AGCTCCAACA	GCAACACCGG	1980
TAGCACAACC	AGCTTCAACA	ACAAATGCAG	TAGCTGCACA	TCCTGAAAAT	GCAGGGCTCC	2040
AACCTCATGT	TGCAGCTTAT	AAAGAAAAAG	TAGCGTCAAC	TTATGGAGTT	AATGAATTCA	2100
GTACATACCG	TGCAGGTGAT	CCAGGTGATC	ATGGTAAAGG	TTTAGCAGTC	GACTTTATTG	2160
TAGGTAAAAA	CCAAGCACTT	GGTAATGAAG	TTGCACAGTA	CTCTACACAA	AATATGGCAG	2220
CAAATAACAT	TTCATATGTT	ATCTGGCAAC	AAAAGTTTTA	CTCAAATACA	AATAGTATTT	2280
ATGGACCTGC	TAATACTTGG	AATGCAATGC	CAGATCGTGG	TGGCGTTACT	GCCAACCATT	2340
ATGACCATGT	TCACGTATCA	TTTAACAAAT	AATATAAAAA	AGGAAGCTAT	TTGGCTTCTT	2400

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TTTTATATGC CTTGAATAGA CTTTCAAGGT TCTTATCTAA TTTTATTAA ATTGAGGAGA 2460
TTAAGCTATA AGTCTGAAAC TACTTTCACG TTAACCGTGA CTAAATCAA ACGTTAAAC 2520
TAAATCTAA GTCTGTAAAG ATTATTGAAA ACGCTTTAAA AACAGATATA ATAAGGTTTG 2580
TAGATATCTA AAATTAAAAA AGATAAGGAA GTGAGAATAT GCCACATCTA AGTAAAGAAG 2640
CTTTTAAAAA GCAAATAAAA AATGGCATT TGTGTCTATG TCAAGCTTTG CCTGGGGAGC 2700
CTCTTTATAC TGAAAGTGGA GGTGTTATGC CTCTTTTAGC TTTGGCAGCT CAAGAAGCAG 2760
GAGCGGTTGG TATAAGAGCC AATAGTGTCC GCGACATTAA GGAAATTCAA GAAGTTACTA 2820
ATTTACCTAT CATCGGCATT ATTAAACGTG AATATCCTCC ACAAGAACCA TTTATCACTG 2880
CTACGATGAC AGAGGTGGAT CAATTAGCTA GTTTAGATAT TGCAGTAATA GCCTTAGATT 2940
GTACACTTAG AGAGCGTCAT GATGGTTTGA GTGTAGCTGA GTTTATTCAA AAGATAAAAG 3000
GGAAATATCC TGAACAGTTG CTAATGGCTG ATATAAGTAC TTTTGAAGAA GGTAAAAATG 3060
CTTTTGAAGC AGGAGTTGAT TTTGTGGGTA CAACTCTATC TGGATACACA GATTACAGCC 3120
GCCAAGAAGA AGGACCGGAT ATAGAACTCC TTAATAAGCT TTGTCAAGCC GGTATAGATG 3180
TGATTGCGGA AGGTAAATT CATACTCCTA AGCAAGCTAA TGAAATTAAT CATATAGGTG 3240
TTGCAGGAAT TGTAGTTGGT GGTGCTATCA CTAGACCAA AGAAATAGCG GAGCGTTTCA 3300
TCTCAGGACT TAGTAAAAG TGTTACTCAA AAATCAAAAT CAAAATAAAA AAGGGGAATA 3360
GTTATGAGTA TCAAAAAAAG TGTGATTGGT TTTGCTTCG GAGCTGCAGC ATTATCAATG 3420
TTTGCTTGTG TAGACAGTAG TCAATCTGTT ATGGCTGCCG AGAAGGATAA AGTCGAAATT 3480
(SEQ ID NO:37)

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FIG. 7a

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NSIWRFFLNK WLVKASSLVV LGGMVLSAGS RVLADTYVRP IDNGRITTGF 50
NGYPGHCGVD YAVPTGTIIR AVADGTVKFA GAGANFSWMT DLAGNCVMIQ 100
HADGMHSGYA HMSRVVARTG EKVKGQDIIG YVGATGMATG PHLHFEFLPA 150
NPNFQNGFHG RINPTSLIAN VATFSGKTQA SAPSIKPLQS APVQNQSSKL 200
KVYRVDELQK VNGVWLKNN TLTPTGFDWN DNGIPASEID EVDANGNLTA 250
DQVLQKGGYF IFNPKTLKTV EKPIQGTAGL TWAKTRFANG SSVWLRVDNS 300
QELLYK (SEQ ID NO:38) 306

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FIG. 7b

MKMNKKVLLT	STMAASLLSV	ASVQAQETDT	TWTARTVSEV	KADLVKQDNK	50
SSYTVKYGDT	LSVISEAMSI	DMNVLAKINN	IADINLIYPE	TTLTVTYDQK	100
SHTATSMKIE	TPATNAAGQT	TATVDLKTNQ	VSVADQKVSL	NTISEGMTPE	150
AATTIVSPMK	TYSSAPALKS	KEVLAQEQAV	SQAAANEQVS	TAPVK SITSE	200
VPAAKEEVKP	TQTSVSQSTT	VSPASVAAET	PAPVAKVAPV	RTVAAPRVAS	250
VKVVT PKVET	GASPEHVSAP	AVPVTTTSTA	TDSKLQATEV	KSVPVAQKAP	300
TATPVAQPAS	TTNAVA AHPE	NAGLQPHVAA	YKEKVASTYG	VNEFSTYRAG	350
DPGDHGKGLA	VDFIVGKNQA	LGNEVAQYST	QNMAANNISY	VIWQQKFYSN	400
TNSIYGPANT	WNAMPDRGGV	TANHVDHVHV	SFNK	(SEQ ID NO:39)	434

FIG. 7c

MPHLSKEAFK	KQIKNGIIVS	CQALPGEPLY	TESGGVMPLL	ALAAQEAGAV	50
GIRANSVRDI	KEIQEVTNLP	IIGIIKREYP	PQEPFITATM	TEVDQLASLD	100
IAVIALDCTL	RERHDGLSVA	EFIQKIKGKY	PEQLLMADIS	TFEEGKNAFE	150
AGVDFVGTTL	SGYTDYXRQE	EGPDIELLNK	LCQAGIDVIA	EGKIHTPKQA	200
NEINHIGVAG	IVVGGAITRP	KEIAERFISG	LS	(SEQ ID NO:40)	232

FIG. 7d

MSIKKSVIGF	CLGAAALSMF	ACVDSSQSVM	AAEKDKVEI	39
(SEQ ID NO:41)				

FIG. 7e



ATGAAAATGA	ATAAAAAGGT	ACTATTGACA	TCGACAATGG	CAGCTTCGCT	50
ATTATCAGTC	GCAAGTGTTT	AAGCACAGA	AACAGATACG	ACGTGGACAG	100
CACGTACTGT	TTCAGAGGTA	AAGGCTGATT	TGGTAAAGCA	AGACAATAAA	150
TCATCATATA	CTGTGAAATA	TGGTGATACA	CTAAGCGTTA	TTTCAGAAGC	200
AATGTCAATT	GATATGAATG	TCTTAGCAAA	AATTAATAAC	ATTGCAGATA	250
TCAATCTTAT	TTATCCTGAG	ACAACACTGA	CAGTAACTTA	CGATCAGAAG	300
AGTCATACTG	CCACTTCAAT	GAAAATAGAA	ACACCAGCAA	CAAATGCTGC	350
TGGTCAAACA	ACAGCTACTG	TGGATTTGAA	AACCAATCAA	GTTTCTGTTG	400
CAGACCAAAA	AGTTTCTCTC	AATACAATTT	CGGAAGGTAT	GACACCAGAA	450
GCAGCAACAA	CGATTGTTTC	GCCAATGAAG	ACATATTCTT	CTGCGCCAGC	500
TTTGAAATCA	AAAGAAGTAT	TAGCACAAGA	GCAAGCTGTT	AGTCAAGCAG	550
CAGCTAATGA	ACAGGTATCA	ACAGCTCCTG	TGAAGTCGAT	TACTTCAGAA	600
GTTCCAGCAG	CTAAAGAGGA	AGTTAAACCA	ACTCAGACGT	CAGTCAGTCA	650
GTCAACAACA	GTATCACCAG	CTTCTGTTGC	CGTGAAACA	CCAGTCCAG	700
TAGCTAAAGT	AGCACCGGTA	AGAAGTGTAG	CAGCCCCTAG	AGTGGCAAGT	750
GTTAAAGTAG	TCACTCCTAA	AGTAGAAACT	GGTGCATCAC	CAGAGCATGT	800
ATCAGCTCCA	GCAGTTCCTG	TGACTACGAC	TTCAACAGCT	ACAGACAGTA	850
AGTTACAAGC	GACTGAAGTT	AAGAGCGTTC	CGGTAGCACA	AAAAGCTCCA	900
ACAGCAACAC	CGGTAGCACA	ACCAGCTTCA	ACAACAAATG	CAGTAGCTGC	950
ACATCCTGAA	AATGCAGGGC	TCCAACCTCA	TGTTGCAGCT	TATAAAGAAA	1000
AAGTAGCGTC	AACTTATGGA	GTTAATGAAT	TCAGTACATA	CCGTGCAGGT	1050
GATCCAGGTG	ATCATGGTAA	AGGTTTAGCA	GTCGACTTTA	TTGTAGGTAA	1100
AAACCAAGCA	CTTGGAATG	AAGTTGCACA	GTAATCTACA	CAAAATATGG	1150
CAGCAAATAA	CATTTTCATAT	GTTATCTGGC	AACAAAAGTT	TTACTCAAAT	1200
ACAAATAGTA	TTTATGGACC	TGCTAATACT	TGGAATGCAA	TGCCAGATCG	1250
TGGTGGCGTT	ACTGCCAACC	ATTATGACCA	TGTTACGTA	TCATTTAACA	1300
AATAA					1305

(SEQ ID NO:42)

FIG. 8

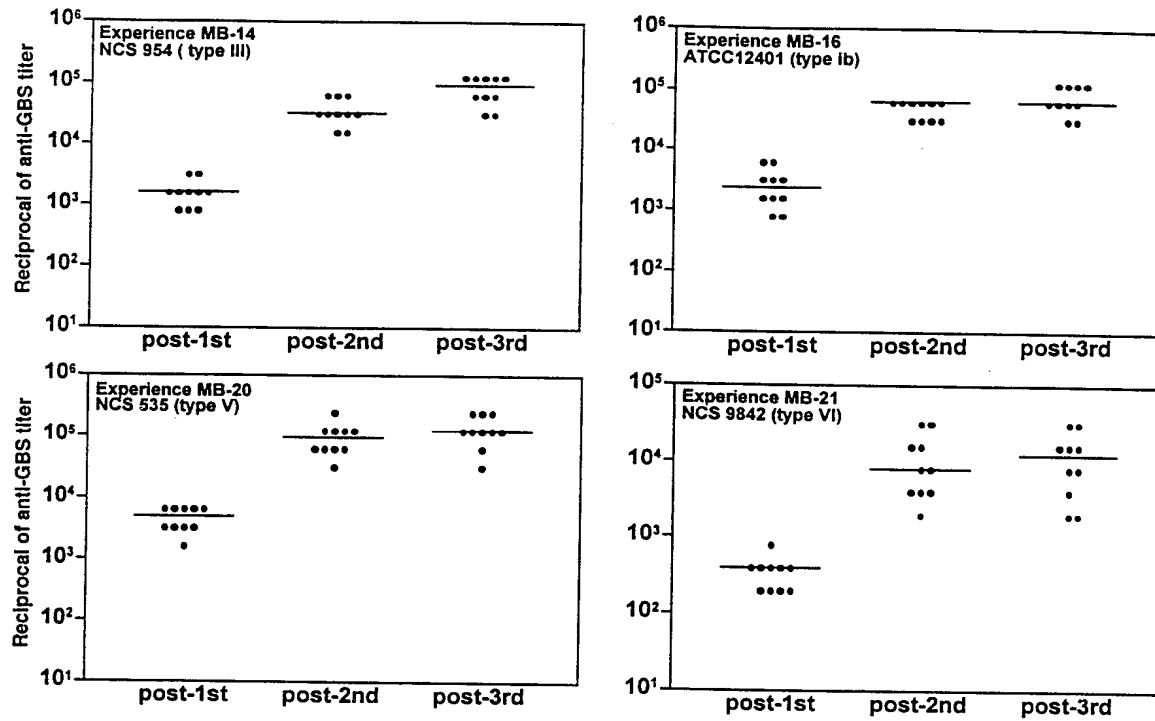
CAAGAAACAG	ATACGACGTG	GACAGCACGT	ACTGTTTCAG	AGGTAAAGGC	50
TGATTTGGTA	AAGCAAGACA	ATAAATCATC	ATATACTGTG	AAATATGGTG	100
ATACACTAAG	CGTTATTTCA	GAAGCAATGT	CAATTGATAT	GAATGTCTTA	150
GCAAAAATTA	ATAACATTGC	AGATATCAAT	CTTATTTATC	CTGAGACAAC	200
ACTGACAGTA	ACTTACGATC	AGAAGAGTCA	TACTGCCACT	TCAATGAAAA	250
TAGAAACACC	AGCAACAAAT	GCTGCTGGTC	AAACAACAGC	TACTGTGGAT	300
TTGAAAACCA	ATCAAGTTTC	TGTTGCAGAC	CAAAAAGTTT	CTCTCAATAC	350
AATTTTCGGAA	GGTATGACAC	CAGAAGCAGC	AACAACGATT	GTTTTCGCCAA	400
TGAAGACATA	TTCTTCTGCG	CCAGCTTTGA	AATCAAAAGA	AGTATTAGCA	450
CAAGAGCAAG	CTGTTAGTCA	AGCAGCAGCT	AATGAACAGG	TATCAACAGC	500
TCCTGTGAAG	TCGATTACTT	CAGAAGTTCC	AGCAGCTAAA	GAGGAAGTTA	550
AACCAACTCA	GACGTCAGTC	AGTCAGTCAA	CAACAGTATC	ACCAGCTTCT	600
GTTGCCGCTG	AAACACCAGC	TCCAGTAGCT	AAAGTAGCAC	CGGTAAGAAC	650
TGTAGCAGCC	CCTAGAGTGG	CAAGTGTAA	AGTAGTCACT	CCTAAAGTAG	700
AAACTGGTGC	ATCACCAGAG	CATGTATCAG	CTCCAGCAGT	TCCTGTGACT	750
ACGACTTCAA	CAGCTACAGA	CAGTAAGTTA	CAAGCGACTG	AAGTTAAGAG	800
CGTTCCGGTA	GCACAAAAAG	CTCCAACAGC	AACACCGGTA	GCACAACCAG	850
CTTCAACAAC	AAATGCAGTA	GCTGCACATC	CTGAAAATGC	AGGGCTCCAA	900
CCTCATGTTG	CAGCTTATAA	AGAAAAAGTA	GCGTCAACTT	ATGGAGTTAA	950
TGAATTCAGT	ACATACCGTG	CAGGTGATCC	AGGTGATCAT	GGTAAAGGTT	1000
TAGCAGTCGA	CTTTATTGTA	GGTAAAAACC	AAGCACTTGG	TAATGAAGTT	1050
GCACAGTACT	CTACACAAAA	TATGGCAGCA	AATAACATTT	CATATGTTAT	1100
CTGGCAACAA	AAGTTTTTACT	CAAATACAAA	TAGTATTTAT	GGACCTGCTA	1150
ATACTTGGA	TGCAATGCCA	GATCGTGGTG	GCGTTACTGC	CAACCATTAT	1200
GACCATGTTC	ACGTATCATT	TAACAAATAA	(SEQ ID NO:43)		1230

FIG. 9

QETDTTWTAR	TVSEVKADLV	KQDNKSSYTV	KYGDTLVIS	EAMSIDMNVL	50
AKINNIADIN	LIYPETTLTV	TYDQKSHTAT	SMKIETPATN	AAGQTTATVD	100
LKTNQVSVAD	QKVS LNTISE	GMTPEAATTI	VSPMKTYSSA	PALKSKEVLA	150
QEQAVSQAAA	NEQVSTAPVK	SITSEVPAAK	EEVKPTQTSV	SQSTTVSPAS	200
VAAETPAPVA	KVAPVRTVAA	PRVASVKVVT	PKVETGASPE	HVSAPAVPVT	250
TTSTATDSKL	QATEVKSVPV	AQKAPTATPV	AQPASTTNAV	AAHPENAGLQ	300
PHVAAYKEKV	ASTYGVNEFS	TYRAGDPGDH	GKGLAVDFIV	GKNQALGNEV	350
AQYSTQNMMA	NNISYVIWQQ	KFYSNTNSIY	GPANTWNAMP	DRGGVTANHY	400
DHVHVSEFNK	(SEQ ID NO:44)				409

FIG. 9a

Fig. 10



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## SEQUENCE LISTING

<110> BioChem Vaccins  
RIOUX, Clément  
DENIS, Martin  
BRODEUR, Bernard R.  
HAMEL, Josée  
CHARLEBOIS, Isabelle  
BOYER, Martine

<120> NOVEL GROUP B STREPTOCOCCUS ANTIGENS

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<150> 60/075,425

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47

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tac ttt att atc cta ttg aca gca tgg act ttg atg gca tta gta act Tyr Phe Ile Ile Leu Leu Thr Ala Trp Thr Leu Met Ala Leu Val Thr 50 55 60	191
gct tta gtg gga tgg gat aat agg tat ggt tcc ttc ttg tcg tta tta Ala Leu Val Gly Trp Asp Asn Arg Tyr Gly Ser Phe Leu Ser Leu Leu 65 70 75	239
ata tta tta ttc cag ctt ggt tca agc gca gga act tac cca ata gaa Ile Leu Leu Phe Gln Leu Gly Ser Ser Ala Gly Thr Tyr Pro Ile Glu 80 85 90 95	287
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Ile Asn Val Leu Leu Val Ala Ile Tyr Gly Ala Leu Thr Val Asp Lys	
240 245 250	
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Lys Ile Leu Leu Lys Gln Gly Leu Pro Ile Leu Ala Leu Leu Thr	
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Phe Leu Phe	
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atataactac gaattcaaaag agaggtgact ttgatt atg act gag aac tgg tta	1041
Met Thr Glu Asn Trp Leu	
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cat act aaa gat ggt tca gat att tat tat cgt gtc gtt ggt caa ggt	1089
His Thr Lys Asp Gly Ser Asp Ile Tyr Tyr Arg Val Val Gly Gln Gly	
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caa ccg att gtt ttt tta cat ggc aat agc tta agt agt cgc tat ttt	1137
Gln Pro Ile Val Phe Leu His Gly Asn Ser Leu Ser Ser Arg Tyr Phe	
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Asp Lys Gln Ile Ala Tyr Phe Ser Lys Tyr Tyr Gln Val Ile Val Met	
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Asp Ser Arg Gly His Gly Lys Ser His Ala Lys Leu Asn Thr Ile Ser	
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Phe Arg Gln Ile Ala Val Asp Leu Lys Asp Ile Leu Val His Leu Glu	
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Ile Asp Lys Val Ile Leu Val Gly His Ser Asp Gly Ala Asn Leu Ala	
360 365 370	
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Leu Val Phe Gln Thr Met Phe Pro Gly Met Val Arg Gly Leu Leu Leu	
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Asn Ser Gly Asn Leu Thr Ile His Gly Gln Arg Trp Trp Asp Ile Leu	
395 400 405	
tta gta agg att gcc tat aaa ttc ctt cac tat tta ggg aaa ctc ttt	1473
Leu Val Arg Ile Ala Tyr Lys Phe Leu His Tyr Leu Gly Lys Leu Phe	
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Pro Tyr Met Arg Gln Lys Ala Gln Val Ile Ser Leu Met Leu Glu Asp	
425 430 435	
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Leu Lys Ile Ser Pro Ala Asp Leu Gln His Val Ser Thr Pro Val Met	
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Val Leu Val Gly Asn Lys Asp Ile Ile Lys Leu Asn His Ser Lys Lys	
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Leu Ala Ser Tyr Phe Pro Arg Gly Glu Phe Tyr Ser Leu Val Gly Phe	
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Gly His His Ile Ile Lys Gln Asp Ser His Val Phe Asn Ile Ile Ala	
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Glu Gln Leu Lys Ser Val Phe Gly Gln Leu Ser Pro Met Asn Leu Phe	
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Leu Ile Ile Leu Val Gly Val Ile Ala Val Leu Pro Thr Thr Gly Tyr	
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Asp Phe Val Leu Asn Gly Leu Leu Arg Thr Asp Lys Ser Lys Arg Tyr	
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Ile Leu Gln Thr Ser Trp Cys Ile Asn Thr Phe Asn Asn Leu Ser Gly	
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Phe Gly Gly Leu Ile Asp Ile Gly Leu Arg Met Ala Phe Tyr Gly Lys	
595 600 605	
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Lys Gly Gln Glu Lys Ser Asp Leu Arg Glu Val Thr Arg Phe Leu Pro	
610 615 620 625	

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Ser His Ile Phe His Ala Lys Ala Ser Val Asp Tyr Tyr Tyr Leu Val	
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Lys Leu Gly Val Val Ser Phe Phe Glu Trp Gly Cys Ala Ala Ala Ala	
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Phe Ile Ile Ile Gly Tyr Leu Met Gly Ile His Leu Pro Val Tyr Lys	
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725 730 735	
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Ile Pro Gly Gly Leu Gly Ser Phe Glu Leu Val Leu Phe Thr Gly Phe	
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Tyr Arg Leu Ala Tyr Tyr Ile Ile Pro Phe Phe Ala Gly Ile Tyr Phe	
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805 810 815	
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820 825 830	
aat att act tat att atg tgg ttg cag aag cta ggc ttg gac cca tta	2830
Asn Ile Thr Tyr Ile Met Trp Leu Gln Lys Leu Gly Leu Asp Pro Leu	
835 840 845	



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870 875 880	
cca att gct att atc tgg att act ttg aca ttg ttt tat ctt aat tta	2974
Pro Ile Ala Ile Ile Trp Ile Thr Leu Thr Leu Phe Tyr Leu Asn Leu	
885 890 895	
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Ser Trp Glu Glu Arg Ile Lys Asp Gly Ile Ile Ile Val Ser Leu Met	
930 935 940 945	
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Gly Val Leu Phe Tyr Ile Ala Gly Leu Leu Phe Pro Ile Arg Ala His	
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965 970 975	
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1190 1195 1200	
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1285 1290 1295	

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Ser Ser Trp Leu Ile Cys Ala Ile Cys Ala Leu Leu Met Glu Asp Ser
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Lys Ile Lys Ile Val Lys
      1330                1335

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Phe Ile Ile Leu Leu Thr Ala Trp Thr Leu Met Ala Leu Val Thr Ala
      50      55      60
Leu Val Gly Trp Asp Asn Arg Tyr Gly Ser Phe Leu Ser Leu Leu Ile
65      70      75      80
Leu Leu Phe Gln Leu Gly Ser Ser Ala Gly Thr Tyr Pro Ile Glu Leu
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Ser Pro Lys Phe Phe Gln Thr Ile Gln Pro Phe Leu Pro Met Thr Tyr
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Ser Val Ser Gly Leu Arg Glu Thr Ile Ser Leu Thr Gly Asp Val Asn
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 Phe Leu Leu Tyr Gly Leu Tyr Ile Ser Gln Asn Gln Glu Ile Val Ala  
 65                                  70                                  75                                  80  
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                                   85                                  90                                  95  
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 Tyr Gln Val Ile Val Met Asp Ser Arg Gly His Gly Lys Ser His Ala  
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 Lys Leu Asn Thr Ile Ser Phe Arg Gln Ile Ala Val Asp Leu Lys Asp  
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 Arg Trp Trp Asp Ile Leu Leu Val Arg Ile Ala Tyr Lys Phe Leu His  
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 Tyr Leu Gly Lys Leu Phe Pro Tyr Met Arg Gln Lys Ala Gln Val Ile  
 145                                  150                                  155                                  160  
 Ser Leu Met Leu Glu Asp Leu Lys Ile Ser Pro Ala Asp Leu Gln His  
                                   165                                  170                                  175  
 Val Ser Thr Pro Val Met Val Leu Val Gly Asn Lys Asp Ile Ile Lys  
           180                                  185                                  190  
 Leu Asn His Ser Lys Lys Leu Ala Ser Tyr Phe Pro Arg Gly Glu Phe  
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 Tyr Ser Leu Val Gly Phe Gly His His Ile Ile Lys Gln Asp Ser His  
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			20					25					30		
Val	Ile	Ala	Val	Leu	Pro	Thr	Thr	Gly	Tyr	Asp	Phe	Val	Leu	Asn	Gly
		35					40					45			
Leu	Leu	Arg	Thr	Asp	Lys	Ser	Lys	Arg	Tyr	Ile	Leu	Gln	Thr	Ser	Trp
	50					55					60				
Cys	Ile	Asn	Thr	Phe	Asn	Asn	Leu	Ser	Gly	Phe	Gly	Gly	Leu	Ile	Asp
65					70					75					80
Ile	Gly	Leu	Arg	Met	Ala	Phe	Tyr	Gly	Lys	Lys	Gly	Gln	Glu	Lys	Ser
			85					90						95	
Asp	Leu	Arg	Glu	Val	Thr	Arg	Phe	Leu	Pro	Tyr	Leu	Ile	Ser	Gly	Leu
			100					105						110	
Ser	Phe	Ile	Ser	Val	Ile	Ala	Leu	Ile	Met	Ser	His	Ile	Phe	His	Ala
		115					120					125			
Lys	Ala	Ser	Val	Asp	Tyr	Tyr	Tyr	Leu	Val	Leu	Ile	Gly	Ala	Ser	Met
	130					135					140				
Tyr	Phe	Pro	Val	Ile	Tyr	Trp	Ile	Ser	Gly	His	Lys	Gly	Ser	His	Tyr
145					150					155					160
Phe	Gly	Asp	Met	Pro	Ser	Ser	Thr	Arg	Ile	Lys	Leu	Gly	Val	Val	Ser
			165					170						175	
Phe	Phe	Glu	Trp	Gly	Cys	Ala	Ala	Ala	Phe	Ile	Ile	Ile	Ile	Gly	Tyr
		180					185					190			
Leu	Met	Gly	Ile	His	Leu	Pro	Val	Tyr	Lys	Ile	Leu	Pro	Leu	Phe	Cys
	195					200						205			
Ile	Gly	Cys	Ala	Val	Gly	Ile	Val	Ser	Leu	Ile	Pro	Gly	Gly	Leu	Gly
	210				215						220				
Ser	Phe	Glu	Leu	Val	Leu	Phe	Thr	Gly	Phe	Ala	Ala	Glu	Gly	Leu	Pro
225					230					235					240
Lys	Glu	Thr	Val	Val	Ala	Trp	Leu	Leu	Leu	Tyr	Arg	Leu	Ala	Tyr	Tyr
			245					250						255	
Ile	Ile	Pro	Phe	Phe	Ala	Gly	Ile	Tyr	Phe	Phe	Ile	His	Tyr	Leu	Gly
		260						265				270			
Ser	Gln	Ile	Asn	Gln	Arg	Tyr	Glu	Asn	Val	Pro	Lys	Glu	Leu	Val	Ser
	275					280						285			
Thr	Val	Leu	Gln	Thr	Met	Val	Ser	His	Leu	Met	Arg	Ile	Leu	Gly	Ala
	290				295						300				
Phe	Leu	Ile	Phe	Ser	Thr	Ala	Phe	Phe	Glu	Asn	Ile	Thr	Tyr	Ile	Met
305					310					315					320
Trp	Leu	Gln	Lys	Leu	Gly	Leu	Asp	Pro	Leu	Gln	Glu	Gln	Met	Leu	Trp
			325						330					335	
Gln	Phe	Pro	Gly	Leu	Leu	Leu	Gly	Val	Cys	Phe	Ile	Leu	Leu	Ala	Arg
		340					345						350		
Thr	Ile	Asp	Gln	Lys	Val	Lys	Asn	Ala	Phe	Pro	Ile	Ala	Ile	Ile	Trp
	355					360						365			
Ile	Thr	Leu	Thr	Leu	Phe	Tyr	Leu	Asn	Leu	Gly	His	Ile	Ser	Trp	Arg
	370				375						380				
Leu	Ser	Phe	Trp	Phe	Ile	Leu	Leu	Leu	Leu	Gly	Leu	Leu	Val	Ile	Lys
385					390					395					400
Pro	Thr	Leu	Tyr	Lys	Gln	Phe	Ile	Tyr	Ser	Trp	Glu	Glu	Arg	Ile	
			405					410					415		
Lys	Asp	Gly	Ile	Ile	Ile	Val	Ser	Leu	Met	Gly	Val	Leu	Phe	Tyr	Ile
			420					425					430		

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Ala Gly Leu Leu Phe Pro Ile Arg Ala His Ile Thr Gly Gly Ser Ile  
 435 440 445  
 Glu Arg Leu His Tyr Ile Ile Ala Trp Glu Pro Ile Ala Leu Ala Thr  
 450 455 460  
 Leu Ile Leu Thr Leu Val Tyr Leu Cys Leu Val Lys Ile Leu Gln Gly  
 465 470 475 480  
 Lys Ser Cys Gln Ile Gly Asp Val Phe Asn Val Asp Arg Tyr Lys Lys  
 485 490 495  
 Leu Leu Gln Ala Tyr Gly Gly Ser Ser Asp Ser Gly Leu Ala Phe Leu  
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 Asn Asp Lys Arg Leu Tyr Trp Tyr Gln Lys Asn Gly Glu Asp Cys Val  
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 Ala Phe Gln Phe Val Ile Val Asn Asn Lys Cys Leu Ile Met Gly Glu  
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 Pro Ala Gly Asp Asp Thr Tyr Ile Arg Glu Ala Ile Glu Ser Phe Ile  
 545 550 555 560  
 Asp Asp Ala Asp Lys Leu Asp Tyr Asp Leu Val Phe Tyr Ser Ile Gly  
 565 570 575  
 Gln Lys Leu Thr Leu Leu Leu His Glu Tyr Gly Phe Asp Phe Met Lys  
 580 585 590  
 Val Gly Glu Asp Ala Leu Val Asn Leu Glu Thr Phe Thr Leu Lys Gly  
 595 600 605  
 Asn Lys Tyr Lys Pro Phe Arg Asn Ala Leu Asn Arg Val Glu Lys Asp  
 610 615 620  
 Gly Phe Tyr Phe Glu Val Val Gln Ser Pro His Ser Gln Glu Leu Leu  
 625 630 635 640  
 Asn Ser Leu Glu Glu Ile Ser Asn Thr Trp Leu Glu Gly Arg Pro Glu  
 645 650 655  
 Lys Gly Phe Ser Leu Gly Tyr Phe Asn Lys Asp Tyr Phe Gln Gln Ala  
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 Pro Ile Ala Leu Val Lys Asn Ala Glu His Glu Val Val Ala Phe Ala  
 675 680 685  
 Asn Ile Met Pro Asn Tyr Glu Lys Ser Ile Ile Ser Ile Asp Leu Met  
 690 695 700  
 Arg His Asp Lys Gln Lys Ile Pro Asn Gly Val Met Asp Phe Leu Phe  
 705 710 715 720  
 Leu Ser Leu Phe Ser Tyr Tyr Gln Glu Lys Gly Tyr His Tyr Phe Asp  
 725 730 735  
 Leu Gly Met Ala Pro Leu Ser Gly Val Gly Arg Val Glu Thr Ser Phe  
 740 745 750  
 Ala Lys Glu Arg Met Ala Tyr Leu Val Tyr His Phe Gly Ser His Phe  
 755 760 765  
 Tyr Ser Phe Asn Gly Leu His Lys Tyr Lys Lys Lys Phe Thr Pro Leu  
 770 775 780  
 Trp Ser Glu Arg Tyr Ile Ser Cys Ser Arg Ser Ser Trp Leu Ile Cys  
 785 790 795 800  
 Ala Ile Cys Ala Leu Leu Met Glu Asp Ser Lys Ile Lys Ile Val Lys  
 805 810 815

&lt;210&gt; 6

&lt;211&gt; 518

&lt;212&gt; PRT

&lt;213&gt; Streptococcus

&lt;400&gt; 6

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Asn	Ile	Thr	Tyr	Ile	Met	Trp	Leu	Gln	Lys	Leu	Gly	Leu	Asp	Pro	Leu
			20					25					30		
Gln	Glu	Gln	Met	Leu	Trp	Gln	Phe	Pro	Gly	Leu	Leu	Leu	Gly	Val	Cys
			35				40					45			
Phe	Ile	Leu	Leu	Ala	Arg	Thr	Ile	Asp	Gln	Lys	Val	Lys	Asn	Ala	Phe
	50					55					60				
Pro	Ile	Ala	Ile	Ile	Trp	Ile	Thr	Leu	Thr	Leu	Phe	Tyr	Leu	Asn	Leu
65					70					75					80
Gly	His	Ile	Ser	Trp	Arg	Leu	Ser	Phe	Trp	Phe	Ile	Leu	Leu	Leu	Leu
				85					90					95	
Gly	Leu	Leu	Val	Ile	Lys	Pro	Thr	Leu	Tyr	Lys	Lys	Gln	Phe	Ile	Tyr
			100					105					110		
Ser	Trp	Glu	Glu	Arg	Ile	Lys	Asp	Gly	Ile	Ile	Ile	Val	Ser	Leu	Met
	115						120					125			
Gly	Val	Leu	Phe	Tyr	Ile	Ala	Gly	Leu	Leu	Phe	Pro	Ile	Arg	Ala	His
	130					135					140				
Ile	Thr	Gly	Gly	Ser	Ile	Glu	Arg	Leu	His	Tyr	Ile	Ile	Ala	Trp	Glu
145					150					155					160
Pro	Ile	Ala	Leu	Ala	Thr	Leu	Ile	Leu	Thr	Leu	Val	Tyr	Leu	Cys	Leu
				165					170					175	
Val	Lys	Ile	Leu	Gln	Gly	Lys	Ser	Cys	Gln	Ile	Gly	Asp	Val	Phe	Asn
			180					185					190		
Val	Asp	Arg	Tyr	Lys	Lys	Leu	Leu	Gln	Ala	Tyr	Gly	Gly	Ser	Ser	Asp
	195						200					205			
Ser	Gly	Leu	Ala	Phe	Leu	Asn	Asp	Lys	Arg	Leu	Tyr	Trp	Tyr	Gln	Lys
	210					215					220				
Asn	Gly	Glu	Asp	Cys	Val	Ala	Phe	Gln	Phe	Val	Ile	Val	Asn	Asn	Lys
225					230					235					240
Cys	Leu	Ile	Met	Gly	Glu	Pro	Ala	Gly	Asp	Asp	Thr	Tyr	Ile	Arg	Glu
				245					250					255	
Ala	Ile	Glu	Ser	Phe	Ile	Asp	Asp	Ala	Asp	Lys	Leu	Asp	Tyr	Asp	Leu
			260					265					270		
Val	Phe	Tyr	Ser	Ile	Gly	Gln	Lys	Leu	Thr	Leu	Leu	Leu	His	Glu	Tyr
	275					280						285			
Gly	Phe	Asp	Phe	Met	Lys	Val	Gly	Glu	Asp	Ala	Leu	Val	Asn	Leu	Glu
	290					295					300				
Thr	Phe	Thr	Leu	Lys	Gly	Asn	Lys	Tyr	Lys	Pro	Phe	Arg	Asn	Ala	Leu
305					310					315					320
Asn	Arg	Val	Glu	Lys	Asp	Gly	Phe	Tyr	Phe	Glu	Val	Val	Gln	Ser	Pro
				325					330					335	
His	Ser	Gln	Glu	Leu	Leu	Asn	Ser	Leu	Glu	Glu	Ile	Ser	Asn	Thr	Trp
			340					345					350		
Leu	Glu	Gly	Arg	Pro	Glu	Lys	Gly	Phe	Ser	Leu	Gly	Tyr	Phe	Asn	Lys
	355						360					365			
Asp	Tyr	Phe	Gln	Gln	Ala	Pro	Ile	Ala	Leu	Val	Lys	Asn	Ala	Glu	His
	370					375					380				
Glu	Val	Val	Ala	Phe	Ala	Asn	Ile	Met	Pro	Asn	Tyr	Glu	Lys	Ser	Ile
385					390					395					400
Ile	Ser	Ile	Asp	Leu	Met	Arg	His	Asp	Lys	Gln	Lys	Ile	Pro	Asn	Gly
				405					410					415	
Val	Met	Asp	Phe	Leu	Phe	Leu	Ser	Leu	Phe	Ser	Tyr	Tyr	Gln	Glu	Lys
			420					425					430		
Gly	Tyr	His	Tyr	Phe	Asp	Leu	Gly	Met	Ala	Pro	Leu	Ser	Gly	Val	Gly
	435						440					445			

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Arg Val Glu Thr Ser Phe Ala Lys Glu Arg Met Ala Tyr Leu Val Tyr
  450                      455                      460
His Phe Gly Ser His Phe Tyr Ser Phe Asn Gly Leu His Lys Tyr Lys
  465                      470                      475                      480
Lys Lys Phe Thr Pro Leu Trp Ser Glu Arg Tyr Ile Ser Cys Ser Arg
                      485                      490                      495
Ser Ser Trp Leu Ile Cys Ala Ile Cys Ala Leu Leu Met Glu Asp Ser
  500                      505                      510
Lys Ile Lys Ile Val Lys
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<212> DNA
<213> Streptococcus

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<222> (1)...(687)

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<221> CDS
<222> (701)...(2557)

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<221> CDS
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<221> CDS
<222> (3106)...(4842)

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<221> CDS
<222> (4850)...(5125)

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  1                      5                      10                      15

tca tta ttg gag aaa ata tct gtt gag cgt tct ttt att gaa ttt gat      96
Ser Leu Leu Glu Lys Ile Ser Val Glu Arg Ser Phe Ile Glu Phe Asp
  20                      25                      30

aaa ctt cta tta gca cct tat tgg cgt aaa gga atg ctg gca cta ata      144
Lys Leu Leu Leu Ala Pro Tyr Trp Arg Lys Gly Met Leu Ala Leu Ile
  35                      40                      45

gat agt cat gct ttt aat tat cta cca tgc tta aaa aat agg gaa tta      192
Asp Ser His Ala Phe Asn Tyr Leu Pro Cys Leu Lys Asn Arg Glu Leu
  50                      55                      60

caa tta agc gcc ttt ttg tcc cag tta gat aaa gat ttt tta ttt gag      240
Gln Leu Ser Ala Phe Leu Ser Gln Leu Asp Lys Asp Phe Leu Phe Glu
  65                      70                      75                      80

aca tca gaa caa gct tgg gca tca ctc atc ttg agt atg gaa gtt gaa      288
Thr Ser Glu Gln Ala Trp Ala Ser Leu Ile Leu Ser Met Glu Val Glu
  85                      90                      95

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cac aca aag act ttt tta aaa aaa tgg aag aca tca act cac ttt caa	336
His Thr Lys Thr Phe Leu Lys Lys Trp Lys Thr Ser Thr His Phe Gln	
100 105 110	
aaa gat gtt gag cat ata gtg gat gtt tat cgt att cgt gaa caa atg	384
Lys Asp Val Glu His Ile Val Asp Val Tyr Arg Ile Arg Glu Gln Met	
115 120 125	
gga ttg gct aaa gaa cat ctt tat cgt tat gga aaa act ata ata aaa	432
Gly Leu Ala Lys Glu His Leu Tyr Arg Tyr Gly Lys Thr Ile Ile Lys	
130 135 140	
caa gcg gaa ggt att cgc aaa gca aga ggc ttg atg gtt gat ttc gaa	480
Gln Ala Glu Gly Ile Arg Lys Ala Arg Gly Leu Met Val Asp Phe Glu	
145 150 155 160	
aaa ata gaa caa cta gat agt gag tta gca atc cat gat agg cat gag	528
Lys Ile Glu Gln Leu Asp Ser Glu Leu Ala Ile His Asp Arg His Glu	
165 170 175	
ata gtt gtc aat ggt ggc acc tta atc aag aaa tta gga ata aaa cct	576
Ile Val Val Asn Gly Gly Thr Leu Ile Lys Lys Leu Gly Ile Lys Pro	
180 185 190	
ggt cca cag atg gga gat att atc tct caa att gaa tta gcc att gtt	624
Gly Pro Gln Met Gly Asp Ile Ile Ser Gln Ile Glu Leu Ala Ile Val	
195 200 205	
tta gga caa ctg att aat gaa gaa gag gct att tta cat ttt gtt aag	672
Leu Gly Gln Leu Ile Asn Glu Glu Ala Ile Leu His Phe Val Lys	
210 215 220	
cag tac ttg atg gat tagagaggat tat atg agc gat ttt tta gta gat	721
Gln Tyr Leu Met Asp Met Ser Asp Phe Leu Val Asp	
225 230 235	
gga ttg act aag tcg gtt ggt gat aag acg gtc ttt agt aat gtt tca	769
Gly Leu Thr Lys Ser Val Gly Asp Lys Thr Val Phe Ser Asn Val Ser	
240 245 250	
ttt atc atc cat agt tta gac cgt att ggg att att ggt gtc aat gga	817
Phe Ile Ile His Ser Leu Asp Arg Ile Gly Ile Ile Gly Val Asn Gly	
255 260 265	
act gga aag aca aca cta tta gat gtt att tcg ggt gaa tta ggt ttt	865
Thr Gly Lys Thr Thr Leu Leu Asp Val Ile Ser Gly Glu Leu Gly Phe	
270 275 280	
gat ggt gat cgt tcc cct ttt tca tca gct aat gat tat aag att gct	913
Asp Gly Asp Arg Ser Pro Phe Ser Ser Ala Asn Asp Tyr Lys Ile Ala	
285 290 295 300	
tat tta aaa caa gaa cca gac ttt gat gat tct cag aca att ttg gac	961
Tyr Leu Lys Gln Glu Pro Asp Phe Asp Asp Ser Gln Thr Ile Leu Asp	
305 310 315	

acc gta ctt tct tct gac tta aga gag atg gct tta att aaa gaa tat	1009
Thr Val Leu Ser Ser Asp Leu Arg Glu Met Ala Leu Ile Lys Glu Tyr	
320 325 330	
gaa tta ttg ctt aat cac tac gaa gaa agt aag caa tca cgt cta gag	1057
Glu Leu Leu Leu Asn His Tyr Glu Glu Ser Lys Gln Ser Arg Leu Glu	
335 340 345	
aaa gta atg gca gaa atg gat tct tta gat gct tgg tct att gag agc	1105
Lys Val Met Ala Glu Met Asp Ser Leu Asp Ala Trp Ser Ile Glu Ser	
350 355 360	
gaa gtc aaa aca gta tta tcc aaa tta ggt att act gat ttg cag ttg	1153
Glu Val Lys Thr Val Ser Lys Leu Gly Ile Thr Asp Leu Gln Leu	
365 370 375 380	
tcg gtt ggt gaa tta tca gga gga tta cga aga cgt gtt caa tta gcg	1201
Ser Val Gly Glu Leu Ser Gly Gly Leu Arg Arg Arg Val Gln Leu Ala	
385 390 395	
caa gta tta tta aat gat gca gat tta ttg ctc tta gac gaa cct act	1249
Gln Val Leu Leu Asn Asp Ala Asp Leu Leu Leu Leu Asp Glu Pro Thr	
400 405 410	
aac cac tta gat att gac act att gca tgg tta acg aat ttt ttg aaa	1297
Asn His Leu Asp Ile Asp Thr Ile Ala Trp Leu Thr Asn Phe Leu Lys	
415 420 425	
aat agt aaa aag aca gtg ctt ttt ata act cat gat cgt tat ttt cta	1345
Asn Ser Lys Lys Thr Val Leu Phe Ile Thr His Asp Arg Tyr Phe Leu	
430 435 440	
gac aat gtt gca aca cgt att ttt gaa tta gat aag gca cag att aca	1393
Asp Asn Val Ala Thr Arg Ile Phe Glu Leu Asp Lys Ala Gln Ile Thr	
445 450 455 460	
gaa tat caa ggc aat tat cag gat tat gtc cga ctt cgt gca gaa caa	1441
Glu Tyr Gln Gly Asn Tyr Gln Asp Tyr Val Arg Leu Arg Ala Glu Gln	
465 470 475	
gac gag cgt gat gct gct agt tta cat aaa aag aaa cag ctt tat aaa	1489
Asp Glu Arg Asp Ala Ala Ser Leu His Lys Lys Lys Gln Leu Tyr Lys	
480 485 490	
cag gaa cta gct tgg atg cgt act cag cca caa gct cgt gca acg aaa	1537
Gln Glu Leu Ala Trp Met Arg Thr Gln Pro Gln Ala Arg Ala Thr Lys	
495 500 505	
caa cag gct cgt att aat cgt ttt caa aat cta aaa aac gat tta cac	1585
Gln Gln Ala Arg Ile Asn Arg Phe Gln Asn Leu Lys Asn Asp Leu His	
510 515 520	
caa aca agc gat aca agc gat ttg gaa atg aca ttt gaa aca agt cga	1633
Gln Thr Ser Asp Thr Ser Asp Leu Glu Met Thr Phe Glu Thr Ser Arg	
525 530 535 540	

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att ggg aaa aag gtt att aat ttt gaa aat gtc tct ttt tct tac cca	1681
Ile Gly Lys Lys Val Ile Asn Phe Glu Asn Val Ser Phe Ser Tyr Pro	
545 550 555	
gat aaa tct atc ttg aaa gac ttt aat ttg tta att caa aat aaa gac	1729
Asp Lys Ser Ile Leu Lys Asp Phe Asn Leu Leu Ile Gln Asn Lys Asp	
560 565 570	
cgt att ggc atc gtt gga gat aat ggt gtt gga aag tca acc tta ctt	1777
Arg Ile Gly Ile Val Gly Asp Asn Gly Val Gly Lys Ser Thr Leu Leu	
575 580 585	
aat tta att gtt caa gat tta cag ccg gat tcg ggt aat gtc tct att	1825
Asn Leu Ile Val Gln Asp Leu Gln Pro Asp Ser Gly Asn Val Ser Ile	
590 595 600	
ggg gaa acg ata cgt gta ggt tac ttt tca caa caa ctt cat aat atg	1873
Gly Glu Thr Ile Arg Val Gly Tyr Phe Ser Gln Gln Leu His Asn Met	
605 610 615 620	
gat ggc tca aaa cgt gtt att aat tat ttg caa gag gtt gca gat gag	1921
Asp Gly Ser Lys Arg Val Ile Asn Tyr Leu Gln Glu Val Ala Asp Glu	
625 630 635	
gtt aaa act agt gtc ggt aca aca agt gtg aca gaa cta ttg gaa caa	1969
Val Lys Thr Ser Val Gly Thr Thr Ser Val Thr Glu Leu Leu Glu Gln	
640 645 650	
ttt ctc ttt cca cgt tcg aca cat gga aca caa att gca aaa tta tca	2017
Phe Leu Phe Pro Arg Ser Thr His Gly Thr Gln Ile Ala Lys Leu Ser	
655 660 665	
ggg ggt gag aaa aaa aga ctt tac ctt tta aaa atc ctg att gaa aag	2065
Gly Gly Glu Lys Lys Arg Leu Tyr Leu Leu Lys Ile Leu Ile Glu Lys	
670 675 680	
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Pro Asn Val Leu Leu Leu Asp Glu Pro Thr Asn Asp Leu Asp Ile Ala	
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Thr Leu Thr Val Leu Glu Asn Phe Leu Gln Gly Phe Gly Gly Pro Val	
705 710 715	
att aca gtt agt cac gat cgt tac ttt tta gat aaa gtg gct aat aaa	2209
Ile Thr Val Ser His Asp Arg Tyr Phe Leu Asp Lys Val Ala Asn Lys	
720 725 730	
att att gcg ttt gaa gat aac gat atc cgt gaa ttt ttt ggt aat tat	2257
Ile Ile Ala Phe Glu Asp Asn Asp Ile Arg Glu Phe Phe Gly Asn Tyr	
735 740 745	
act gat tat tta gat gaa aaa gca ttt aat gag caa aat aat gaa gtt	2305
Thr Asp Tyr Leu Asp Glu Lys Ala Phe Asn Glu Gln Asn Asn Glu Val	
750 755 760	

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aaa aga atg tct tac ttt gaa aaa caa gaa tgg gcg aca att gaa gac Lys Arg Met Ser Tyr Phe Glu Lys Gln Glu Trp Ala Thr Ile Glu Asp 785 790 795	2401
gat att atg ata ttg gaa aat act atc act cgt ata gaa aat gat atg Asp Ile Met Ile Leu Glu Asn Thr Ile Thr Arg Ile Glu Asn Asp Met 800 805 810	2449
caa aca tgt ggt agt gat ttt aca agg tta tct gat tta caa aag gaa Gln Thr Cys Gly Ser Asp Phe Thr Arg Leu Ser Asp Leu Gln Lys Glu 815 820 825	2497
tta gat gca aaa aat gaa gca ctt cta gaa aag tat gac cgt tat gag Leu Asp Ala Lys Asn Glu Ala Leu Leu Glu Lys Tyr Asp Arg Tyr Glu 830 835 840	2545
tac ctt agt gag ttagacac atg att atc cgt ccg att att aaa aat gat Tyr Leu Ser Glu LeuAspThrMet Ile Ile Arg Pro Ile Ile Lys Asn Asp 845 850 855 860	2595
gac caa gca gtt gca caa tta att cga caa agt tta cgc gcc tat gat Asp Gln Ala Val Ala Gln Leu Ile Arg Gln Ser Leu Arg Ala Tyr Asp 865 870 875	2643
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gag aga gat gag att att ggc tgt ggc ggc ttt ggt ccg ctg aaa aat Glu Arg Asp Glu Ile Ile Gly Cys Gly Gly Phe Gly Pro Leu Lys Asn 910 915 920 925	2787
cta att gca gag atg cag aag gtg tac att gca gaa cgt ttc cgt ggt Leu Ile Ala Glu Met Gln Lys Val Tyr Ile Ala Glu Arg Phe Arg Gly 930 935 940	2835
aag ggg ctt gct act gat tta gtg aaa atg att gaa gta gaa gct cga Lys Gly Leu Ala Thr Asp Leu Val Lys Met Ile Glu Val Glu Ala Arg 945 950 955	2883
aaa att ggg tat aga caa ctt tat tta gag aca gcc agt act ttg agt Lys Ile Gly Tyr Arg Gln Leu Tyr Leu Glu Thr Ala Ser Thr Leu Ser 960 965 970	2931
agg gca act gcg gtt tat aag cat atg gga tat tgt gcc tta tcg caa Arg Ala Thr Ala Val Tyr Lys His Met Gly Tyr Cys Ala Leu Ser Gln 975 980 985	2979

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cca ata gca aat gat caa ggt cat aca gct atg gat att tgg atg att 3027  
 Pro Ile Ala Asn Asp Gln Gly His Thr Ala Met Asp Ile Trp Met Ile  
 990 995 1000 1005

aaa gat tta taagttgaaa gtggattagt gaacatggat taattatattt 3076  
 Lys Asp Leu

gagataagag gaaagaaaag gagacatat atg gca tat att tgg tct tat ttg 3129  
 Met Ala Tyr Ile Trp Ser Tyr Leu  
 1010 1015

aaa agg tac ccc aat tgg tta tgg ctt gat tta cta gga gct atg ctt 3177  
 Lys Arg Tyr Pro Asn Trp Leu Trp Leu Asp Leu Leu Gly Ala Met Leu  
 1020 1025 1030

ttt gtg acg gtt atc cta gga atg ccc aca gcc tta gcg ggt atg att 3225  
 Phe Val Thr Val Ile Leu Gly Met Pro Thr Ala Leu Ala Gly Met Ile  
 1035 1040 1045

gat aat ggc gtt aca aaa ggt gat cgg act gga gtt tat ctg tgg acg 3273  
 Asp Asn Gly Val Thr Lys Gly Asp Arg Thr Gly Val Tyr Leu Trp Thr  
 1050 1055 1060

ttc atc atg ttt ata ttt gtt gta cta ggt att att ggg cgt att acg 3321  
 Phe Ile Met Phe Ile Phe Val Val Leu Gly Ile Ile Gly Arg Ile Thr  
 1065 1070 1075 1080

atg gct tac gca tct agt cgc tta acg aca aca atg att aga gat atg 3369  
 Met Ala Tyr Ala Ser Arg Leu Thr Thr Met Ile Arg Asp Met  
 1085 1090 1095

cgt aat gat atg tat gct aag ctt caa gaa tac tcc cat cat gaa tat 3417  
 Arg Asn Asp Met Tyr Ala Lys Leu Gln Glu Tyr Ser His His Glu Tyr  
 1100 1105 1110

gaa cag ata ggt gta tct tca cta gtg aca cgt atg aca agc gat act 3465  
 Glu Gln Ile Gly Val Ser Ser Leu Val Thr Arg Met Thr Ser Asp Thr  
 1115 1120 1125

ttt gtt ttg atg caa ttt gct gaa atg tct tta cgt tta ggc cta gta 3513  
 Phe Val Leu Met Gln Phe Ala Glu Met Ser Leu Arg Leu Gly Leu Val  
 1130 1135 1140

act cct atg gta atg att ttt agc gtg gtt atg ata cta att acg agt 3561  
 Thr Pro Met Val Met Ile Phe Ser Val Val Met Ile Leu Ile Thr Ser  
 1145 1150 1155 1160

cca tct ttg gct tgg ctt gta gcg gtt gcg atg cct ctt ttg gta gga 3609  
 Pro Ser Leu Ala Trp Leu Val Ala Val Ala Met Pro Leu Leu Val Gly  
 1165 1170 1175

gtc gtt tta tat gta gct ata aaa aca aaa cct tta tct gaa aga caa 3657  
 Val Val Leu Tyr Val Ala Ile Lys Thr Lys Pro Leu Ser Glu Arg Gln  
 1180 1185 1190

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cag act atg ctt gat aaa atc aat caa tat gtt cgt gaa aat tta aca Gln Thr Met Leu Asp Lys Ile Asn Gln Tyr Val Arg Glu Asn Leu Thr 1195 1200 1205	3705
ggg tta cgc gtt gtt aga gcc ttt gca aga gag aat ttt caa tca caa Gly Leu Arg Val Val Arg Ala Phe Ala Arg Glu Asn Phe Gln Ser Gln 1210 1215 1220	3753
aaa ttt caa gtc gct aac caa cgt tac aca gat act tca act ggt ctt Lys Phe Gln Val Ala Asn Gln Arg Tyr Thr Asp Thr Ser Thr Gly Leu 1225 1230 1235 1240	3801
ttt aaa tta aca ggg cta aca gaa cca ctt ttc gtt caa att att att Phe Lys Leu Thr Gly Leu Thr Glu Pro Leu Phe Val Gln Ile Ile Ile 1245 1250 1255	3849
gca atg att gtg gct atc gtt tgg ttt gct ttg gat ccc tta caa aga Ala Met Ile Val Ala Ile Val Trp Phe Ala Leu Asp Pro Leu Gln Arg 1260 1265 1270	3897
ggt gct att aaa ata ggg gat tta gtt gct ttt atc gaa tat agc ttc Gly Ala Ile Lys Ile Gly Asp Leu Val Ala Phe Ile Glu Tyr Ser Phe 1275 1280 1285	3945
cat gct ctc ttt tca ttt ttg cta ttt gcc aat ctt ttt act atg tat His Ala Leu Phe Ser Phe Leu Leu Phe Ala Asn Leu Phe Thr Met Tyr 1290 1295 1300	3993
cct cgt atg gtg gta tca agc cat cgt att aga gag gtg atg gat atg Pro Arg Met Val Val Ser Ser His Arg Ile Arg Glu Val Met Asp Met 1305 1310 1315 1320	4041
cca atc tct atc aat cct aat gcc gaa ggt gtt acg gat acg aaa ctt Pro Ile Ser Ile Asn Pro Asn Ala Glu Gly Val Thr Asp Thr Lys Leu 1325 1330 1335	4089
aaa ggg cat tta gaa ttt gat aat gta aca ttc gct tat cca gga gaa Lys Gly His Leu Glu Phe Asp Asn Val Thr Phe Ala Tyr Pro Gly Glu 1340 1345 1350	4137
aca gag agt ccc gtt ttg cat gat att tct ttt aaa gct aag cct gga Thr Glu Ser Pro Val Leu His Asp Ile Ser Phe Lys Ala Lys Pro Gly 1355 1360 1365	4185
gaa aca att gct ttt att ggt tca aca ggt tca gga aaa tct tct ctt Glu Thr Ile Ala Phe Ile Gly Ser Thr Gly Ser Gly Lys Ser Ser Leu 1370 1375 1380	4233
ggt aat ttg att cca cgt ttt tat gat gtg aca ctt gga aaa atc tta Val Asn Leu Ile Pro Arg Phe Tyr Asp Val Thr Leu Gly Lys Ile Leu 1385 1390 1395 1400	4281
gta gat gga gtt gat gta aga gat tat aac ctt aaa tca ctt cgc caa Val Asp Gly Val Asp Val Arg Asp Tyr Asn Leu Lys Ser Leu Arg Gln 1405 1410 1415	4329

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aag att gga ttt atc ccc caa aaa gct ctt tta ttt aca ggg aca ata Lys Ile Gly Phe Ile Pro Gln Lys Ala Leu Leu Phe Thr Gly Thr Ile 1420 1425 1430	4377
gga gag aat tta aaa tat gga aaa gct gat gct act att gat gat ctt Gly Glu Asn Leu Lys Tyr Gly Lys Ala Asp Ala Thr Ile Asp Asp Leu 1435 1440 1445	4425
aga caa gcg gtt gat att tct caa gct aaa gag ttt att gag agt cac Arg Gln Ala Val Asp Ile Ser Gln Ala Lys Glu Phe Ile Glu Ser His 1450 1455 1460	4473
caa gaa gcc ttt gaa acg cat tta gct gaa ggt ggg agc aat ctt tct Gln Glu Ala Phe Glu Thr His Leu Ala Glu Gly Gly Ser Asn Leu Ser 1465 1470 1475 1480	4521
ggg ggt caa aaa caa cgg tta tct att gct agg gct gtt gtt aaa gat Gly Gly Gln Lys Gln Arg Leu Ser Ile Ala Arg Ala Val Val Lys Asp 1485 1490 1495	4569
cca gat tta tat att ttt gat gat tca ttt tct gct ctc gat tat aag Pro Asp Leu Tyr Ile Phe Asp Asp Ser Phe Ser Ala Leu Asp Tyr Lys 1500 1505 1510	4617
aca gac gct act tta aga gcg cgt cta aaa gaa gta acc ggt gat tct Thr Asp Ala Thr Leu Arg Ala Arg Leu Lys Glu Val Thr Gly Asp Ser 1515 1520 1525	4665
aca gtt ttg ata gtt gct caa agg gtg ggt acg att atg gat gct gat Thr Val Leu Ile Val Ala Gln Arg Val Gly Thr Ile Met Asp Ala Asp 1530 1535 1540	4713
cag att att gtc ctt gat gaa ggc gaa att gtc ggt cgt ggt acc cac Gln Ile Ile Val Leu Asp Glu Gly Glu Ile Val Gly Arg Gly Thr His 1545 1550 1555 1560	4761
gct caa tta ata gaa aat aat gct att tat cgt gaa atc gct gag tca Ala Gln Leu Ile Glu Asn Asn Ala Ile Tyr Arg Glu Ile Ala Glu Ser 1565 1570 1575	4809
caa ctg aag aac caa aac tta tca gaa gga gag tgattgt atg aga aaa Gln Leu Lys Asn Gln Asn Leu Ser Glu Gly Glu Met Arg Lys 1580 1585 1590	4858
aaa tct gtt ttt ttg aga tta tgg tct tac cta act cgc tac aaa gct Lys Ser Val Phe Leu Arg Leu Trp Ser Tyr Leu Thr Arg Tyr Lys Ala 1595 1600 1605	4906
act ctt ttc tta gcg att ttt ttg aaa gtt tta tct agt ttt atg agt Thr Leu Phe Leu Ala Ile Phe Leu Lys Val Leu Ser Ser Phe Met Ser 1610 1615 1620	4954
gtt ctg gag cct ttt att tta ggg tta gcg ata aca gag ttg act gct Val Leu Glu Pro Phe Ile Leu Gly Leu Ala Ile Thr Glu Leu Thr Ala 1625 1630 1635	5002

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aac ctt gtt gat atg gct aag gga gtt tct ggg gca gaa ttg aac gtt      5050
Asn Leu Val Asp Met Ala Lys Gly Val Ser Gly Ala Glu Leu Asn Val
1640                      1645                      1650

cct tat att gct ggt att ttg att att tat ttt ttc aga ggt gtt ttc      5098
Pro Tyr Ile Ala Gly Ile Leu Ile Ile Tyr Phe Phe Arg Gly Val Phe
1655                      1660                      1665                      1670

tat gaa tta ggt tct tat ggc tca aat t                                5126
Tyr Glu Leu Gly Ser Tyr Gly Ser Asn
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<210> 8
<211> 229
<212> PRT
<213> Streptococcus

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20     25     30
Lys Leu Leu Leu Ala Pro Tyr Trp Arg Lys Gly Met Leu Ala Leu Ile
35     40     45
Asp Ser His Ala Phe Asn Tyr Leu Pro Cys Leu Lys Asn Arg Glu Leu
50     55     60
Gln Leu Ser Ala Phe Leu Ser Gln Leu Asp Lys Asp Phe Leu Phe Glu
65     70     75     80
Thr Ser Glu Gln Ala Trp Ala Ser Leu Ile Leu Ser Met Glu Val Glu
85     90     95
His Thr Lys Thr Phe Leu Lys Lys Trp Lys Thr Ser Thr His Phe Gln
100    105    110
Lys Asp Val Glu His Ile Val Asp Val Tyr Arg Ile Arg Glu Gln Met
115    120    125
Gly Leu Ala Lys Glu His Leu Tyr Arg Tyr Gly Lys Thr Ile Ile Lys
130    135    140
Gln Ala Glu Gly Ile Arg Lys Ala Arg Gly Leu Met Val Asp Phe Glu
145    150    155    160
Lys Ile Glu Gln Leu Asp Ser Glu Leu Ala Ile His Asp Arg His Glu
165    170    175
Ile Val Val Asn Gly Gly Thr Leu Ile Lys Lys Leu Gly Ile Lys Pro
180    185    190
Gly Pro Gln Met Gly Asp Ile Ile Ser Gln Ile Glu Leu Ala Ile Val
195    200    205
Leu Gly Gln Leu Ile Asn Glu Glu Ala Ile Leu His Phe Val Lys
210    215    220
Gln Tyr Leu Met Asp
225

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<210> 9
<211> 622
<212> PRT
<213> Streptococcus

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<400> 9

Met	Ser	Asp	Phe	Leu	Val	Asp	Gly	Leu	Thr	Lys	Ser	Val	Gly	Asp	Lys
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			20					25					30		
Gly	Ile	Ile	Gly	Val	Asn	Gly	Thr	Gly	Lys	Thr	Thr	Leu	Leu	Asp	Val
		35					40					45			
Ile	Ser	Gly	Glu	Leu	Gly	Phe	Asp	Gly	Asp	Arg	Ser	Pro	Phe	Ser	Ser
	50				55						60				
Ala	Asn	Asp	Tyr	Lys	Ile	Ala	Tyr	Leu	Lys	Gln	Glu	Pro	Asp	Phe	Asp
65				70						75					80
Asp	Ser	Gln	Thr	Ile	Leu	Asp	Thr	Val	Leu	Ser	Ser	Asp	Leu	Arg	Glu
			85					90						95	
Met	Ala	Leu	Ile	Lys	Glu	Tyr	Glu	Leu	Leu	Leu	Asn	His	Tyr	Glu	Glu
			100				105						110		
Ser	Lys	Gln	Ser	Arg	Leu	Glu	Lys	Val	Met	Ala	Glu	Met	Asp	Ser	Leu
		115					120					125			
Asp	Ala	Trp	Ser	Ile	Glu	Ser	Glu	Val	Lys	Thr	Val	Leu	Ser	Lys	Leu
	130					135					140				
Gly	Ile	Thr	Asp	Leu	Gln	Leu	Ser	Val	Gly	Glu	Leu	Ser	Gly	Gly	Leu
145				150						155					160
Arg	Arg	Arg	Val	Gln	Leu	Ala	Gln	Val	Leu	Leu	Asn	Asp	Ala	Asp	Leu
			165					170						175	
Leu	Leu	Leu	Asp	Glu	Pro	Thr	Asn	His	Leu	Asp	Ile	Asp	Thr	Ile	Ala
			180					185					190		
Trp	Leu	Thr	Asn	Phe	Leu	Lys	Asn	Ser	Lys	Lys	Thr	Val	Leu	Phe	Ile
	195						200					205			
Thr	His	Asp	Arg	Tyr	Phe	Leu	Asp	Asn	Val	Ala	Thr	Arg	Ile	Phe	Glu
	210					215					220				
Leu	Asp	Lys	Ala	Gln	Ile	Thr	Glu	Tyr	Gln	Gly	Asn	Tyr	Gln	Asp	Tyr
225				230						235					240
Val	Arg	Leu	Arg	Ala	Glu	Gln	Asp	Glu	Arg	Asp	Ala	Ala	Ser	Leu	His
			245						250					255	
Lys	Lys	Lys	Gln	Leu	Tyr	Lys	Gln	Glu	Leu	Ala	Trp	Met	Arg	Thr	Gln
			260					265					270		
Pro	Gln	Ala	Arg	Ala	Thr	Lys	Gln	Gln	Ala	Arg	Ile	Asn	Arg	Phe	Gln
		275					280					285			
Asn	Leu	Lys	Asn	Asp	Leu	His	Gln	Thr	Ser	Asp	Thr	Ser	Asp	Leu	Glu
	290				295						300				
Met	Thr	Phe	Glu	Thr	Ser	Arg	Ile	Gly	Lys	Lys	Val	Ile	Asn	Phe	Glu
305				310						315					320
Asn	Val	Ser	Phe	Ser	Tyr	Pro	Asp	Lys	Ser	Ile	Leu	Lys	Asp	Phe	Asn
			325					330						335	
Leu	Leu	Ile	Gln	Asn	Lys	Asp	Arg	Ile	Gly	Ile	Val	Gly	Asp	Asn	Gly
		340						345					350		
Val	Gly	Lys	Ser	Thr	Leu	Leu	Asn	Leu	Ile	Val	Gln	Asp	Leu	Gln	Pro
		355					360					365			
Asp	Ser	Gly	Asn	Val	Ser	Ile	Gly	Glu	Thr	Ile	Arg	Val	Gly	Tyr	Phe
	370					375					380				
Ser	Gln	Gln	Leu	His	Asn	Met	Asp	Gly	Ser	Lys	Arg	Val	Ile	Asn	Tyr
385				390						395					400
Leu	Gln	Glu	Val	Ala	Asp	Glu	Val	Lys	Thr	Ser	Val	Gly	Thr	Thr	Ser
			405					410						415	
Val	Thr	Glu	Leu	Leu	Glu	Gln	Phe	Leu	Phe	Pro	Arg	Ser	Thr	His	Gly
			420					425						430	

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Thr Gln Ile Ala Lys Leu Ser Gly Gly Glu Lys Lys Arg Leu Tyr Leu  
 435 440 445  
 Leu Lys Ile Leu Ile Glu Lys Pro Asn Val Leu Leu Leu Asp Glu Pro  
 450 455 460  
 Thr Asn Asp Leu Asp Ile Ala Thr Leu Thr Val Leu Glu Asn Phe Leu  
 465 470 475 480  
 Gln Gly Phe Gly Gly Pro Val Ile Thr Val Ser His Asp Arg Tyr Phe  
 485 490 495  
 Leu Asp Lys Val Ala Asn Lys Ile Ile Ala Phe Glu Asp Asn Asp Ile  
 500 505 510  
 Arg Glu Phe Phe Gly Asn Tyr Thr Asp Tyr Leu Asp Glu Lys Ala Phe  
 515 520 525  
 Asn Glu Gln Asn Asn Glu Val Ile Ser Lys Lys Glu Ser Thr Lys Thr  
 530 535 540  
 Ser Arg Glu Lys Gln Ser Arg Lys Arg Met Ser Tyr Phe Glu Lys Gln  
 545 550 555 560  
 Glu Trp Ala Thr Ile Glu Asp Asp Ile Met Ile Leu Glu Asn Thr Ile  
 565 570 575  
 Thr Arg Ile Glu Asn Asp Met Gln Thr Cys Gly Ser Asp Phe Thr Arg  
 580 585 590  
 Leu Ser Asp Leu Gln Lys Glu Leu Asp Ala Lys Asn Glu Ala Leu Leu  
 595 600 605  
 Glu Lys Tyr Asp Arg Tyr Glu Tyr Leu Ser Glu Leu Asp Thr  
 610 615 620

&lt;210&gt; 10

&lt;211&gt; 157

&lt;212&gt; PRT

&lt;213&gt; Streptococcus

&lt;400&gt; 10

Met Ile Ile Arg Pro Ile Ile Lys Asn Asp Asp Gln Ala Val Ala Gln  
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 Leu Ile Arg Gln Ser Leu Arg Ala Tyr Asp Leu Asp Lys Pro Asp Thr  
 20 25 30  
 Ala Tyr Ser Asp Pro His Leu Asp His Leu Thr Ser Tyr Tyr Glu Lys  
 35 40 45  
 Ile Glu Lys Ser Gly Phe Phe Val Ile Glu Glu Arg Asp Glu Ile Ile  
 50 55 60  
 Gly Cys Gly Gly Phe Gly Pro Leu Lys Asn Leu Ile Ala Glu Met Gln  
 65 70 75 80  
 Lys Val Tyr Ile Ala Glu Arg Phe Arg Gly Lys Gly Leu Ala Thr Asp  
 85 90 95  
 Leu Val Lys Met Ile Glu Val Glu Ala Arg Lys Ile Gly Tyr Arg Gln  
 100 105 110  
 Leu Tyr Leu Glu Thr Ala Ser Thr Leu Ser Arg Ala Thr Ala Val Tyr  
 115 120 125  
 Lys His Met Gly Tyr Cys Ala Leu Ser Gln Pro Ile Ala Asn Asp Gln  
 130 135 140  
 Gly His Thr Ala Met Asp Ile Trp Met Ile Lys Asp Leu  
 145 150 155

&lt;210&gt; 11

&lt;211&gt; 579

&lt;212&gt; PRT

&lt;213&gt; Streptococcus

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          20          25          30
Pro  Thr  Ala  Leu  Ala  Gly  Met  Ile  Asp  Asn  Gly  Val  Thr  Lys  Gly  Asp
          35          40          45
Arg  Thr  Gly  Val  Tyr  Leu  Trp  Thr  Phe  Ile  Met  Phe  Ile  Phe  Val  Val
 50          55          60
Leu  Gly  Ile  Ile  Gly  Arg  Ile  Thr  Met  Ala  Tyr  Ala  Ser  Ser  Arg  Leu
 65          70          75          80
Thr  Thr  Thr  Met  Ile  Arg  Asp  Met  Arg  Asn  Asp  Met  Tyr  Ala  Lys  Leu
          85          90          95
Gln  Glu  Tyr  Ser  His  His  Glu  Tyr  Glu  Gln  Ile  Gly  Val  Ser  Ser  Leu
          100          105          110
Val  Thr  Arg  Met  Thr  Ser  Asp  Thr  Phe  Val  Leu  Met  Gln  Phe  Ala  Glu
          115          120          125
Met  Ser  Leu  Arg  Leu  Gly  Leu  Val  Thr  Pro  Met  Val  Met  Ile  Phe  Ser
          130          135          140
Val  Val  Met  Ile  Leu  Ile  Thr  Ser  Pro  Ser  Leu  Ala  Trp  Leu  Val  Ala
 145          150          155          160
Val  Ala  Met  Pro  Leu  Leu  Val  Gly  Val  Val  Leu  Tyr  Val  Ala  Ile  Lys
          165          170          175
Thr  Lys  Pro  Leu  Ser  Glu  Arg  Gln  Gln  Thr  Met  Leu  Asp  Lys  Ile  Asn
          180          185          190
Gln  Tyr  Val  Arg  Glu  Asn  Leu  Thr  Gly  Leu  Arg  Val  Val  Arg  Ala  Phe
          195          200          205
Ala  Arg  Glu  Asn  Phe  Gln  Ser  Gln  Lys  Phe  Gln  Val  Ala  Asn  Gln  Arg
          210          215          220
Tyr  Thr  Asp  Thr  Ser  Thr  Gly  Leu  Phe  Lys  Leu  Thr  Gly  Leu  Thr  Glu
 225          230          235          240
Pro  Leu  Phe  Val  Gln  Ile  Ile  Ile  Ala  Met  Ile  Val  Ala  Ile  Val  Trp
          245          250          255
Phe  Ala  Leu  Asp  Pro  Leu  Gln  Arg  Gly  Ala  Ile  Lys  Ile  Gly  Asp  Leu
          260          265          270
Val  Ala  Phe  Ile  Glu  Tyr  Ser  Phe  His  Ala  Leu  Phe  Ser  Phe  Leu  Leu
          275          280          285
Phe  Ala  Asn  Leu  Phe  Thr  Met  Tyr  Pro  Arg  Met  Val  Val  Ser  Ser  His
          290          295          300
Arg  Ile  Arg  Glu  Val  Met  Asp  Met  Pro  Ile  Ser  Ile  Asn  Pro  Asn  Ala
 305          310          315          320
Glu  Gly  Val  Thr  Asp  Thr  Lys  Leu  Lys  Gly  His  Leu  Glu  Phe  Asp  Asn
          325          330          335
Val  Thr  Phe  Ala  Tyr  Pro  Gly  Glu  Thr  Glu  Ser  Pro  Val  Leu  His  Asp
          340          345          350
Ile  Ser  Phe  Lys  Ala  Lys  Pro  Gly  Glu  Thr  Ile  Ala  Phe  Ile  Gly  Ser
          355          360          365
Thr  Gly  Ser  Gly  Lys  Ser  Ser  Leu  Val  Asn  Leu  Ile  Pro  Arg  Phe  Tyr
          370          375          380
Asp  Val  Thr  Leu  Gly  Lys  Ile  Leu  Val  Asp  Gly  Val  Asp  Val  Arg  Asp
 385          390          395          400
Tyr  Asn  Leu  Lys  Ser  Leu  Arg  Gln  Lys  Ile  Gly  Phe  Ile  Pro  Gln  Lys
          405          410          415
Ala  Leu  Leu  Phe  Thr  Gly  Thr  Ile  Gly  Glu  Asn  Leu  Lys  Tyr  Gly  Lys
          420          425          430

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Ala Asp Ala Thr Ile Asp Asp Leu Arg Gln Ala Val Asp Ile Ser Gln  
 435 440 445  
 Ala Lys Glu Phe Ile Glu Ser His Gln Glu Ala Phe Glu Thr His Leu  
 450 455 460  
 Ala Glu Gly Gly Ser Asn Leu Ser Gly Gly Gln Lys Gln Arg Leu Ser  
 465 470 475 480  
 Ile Ala Arg Ala Val Val Lys Asp Pro Asp Leu Tyr Ile Phe Asp Asp  
 485 490 495  
 Ser Phe Ser Ala Leu Asp Tyr Lys Thr Asp Ala Thr Leu Arg Ala Arg  
 500 505 510  
 Leu Lys Glu Val Thr Gly Asp Ser Thr Val Leu Ile Val Ala Gln Arg  
 515 520 525  
 Val Gly Thr Ile Met Asp Ala Asp Gln Ile Ile Val Leu Asp Glu Gly  
 530 535 540  
 Glu Ile Val Gly Arg Gly Thr His Ala Gln Leu Ile Glu Asn Asn Ala  
 545 550 555 560  
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 565 570 575  
 Glu Gly Glu

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 Phe Met Ser Val Leu Glu Pro Phe Ile Leu Gly Leu Ala Ile Thr Glu  
 35 40 45  
 Leu Thr Ala Asn Leu Val Asp Met Ala Lys Gly Val Ser Gly Ala Glu  
 50 55 60  
 Leu Asn Val Pro Tyr Ile Ala Gly Ile Leu Ile Ile Tyr Phe Phe Arg  
 65 70 75 80  
 Gly Val Phe Tyr Glu Leu Gly Ser Tyr Gly Ser Asn  
 85 90

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<221> CDS

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<222> (2946)...(2716)  
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 gaa gaa aac ata tgg tta tat cgg ctg agt tgc tgc cat ttt act agc	95
Glu Glu Asn Ile Trp Leu Tyr Arg Leu Ser Cys Cys His Phe Thr Ser	
20 25 30	
 tac tca tat tgg aag tta cca act tgg taagcatcat atg ggt cta gca	144
Tyr Ser Tyr Trp Lys Leu Pro Thr Trp Met Gly Leu Ala	
35 40	
 aca aag gac aat cag att gcc tat att gat gac agc aaa ggt aag gca	192
Thr Lys Asp Asn Gln Ile Ala Tyr Ile Asp Asp Ser Lys Gly Lys Ala	
45 50 55 60	
 aaa gcc cct aaa aca aac aaa acg atg gat caa atc agt gct gaa gaa	240
Lys Ala Pro Lys Thr Asn Lys Thr Met Asp Gln Ile Ser Ala Glu Glu	
65 70 75	
 ggc atc tct gct gaa cag atc gta gtc aaa att act gac caa ggc tat	288
Gly Ile Ser Ala Glu Gln Ile Val Val Lys Ile Thr Asp Gln Gly Tyr	
80 85 90	
 gtg acc tca cac ggt gac cat tat cat ttt tac aat ggg aaa gtt cct	336
Val Thr Ser His Gly Asp His Tyr His Phe Tyr Asn Gly Lys Val Pro	
95 100 105	
 tat gat gcg att att agt gaa gag ttg ttg atg acg gat cct aat tac	384
Tyr Asp Ala Ile Ile Ser Glu Glu Leu Leu Met Thr Asp Pro Asn Tyr	
110 115 120	
 cgt ttt aaa caa tca gac gtt atc aat gaa atc tta gac ggt tac gtt	432
Arg Phe Lys Gln Ser Asp Val Ile Asn Glu Ile Leu Asp Gly Tyr Val	
125 130 135 140	

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att aaa gtc aat ggc aac tat tat gtt tac ctc aag cca ggt agt aag	480
Ile Lys Val Asn Gly Asn Tyr Tyr Val Tyr Leu Lys Pro Gly Ser Lys	
145 150 155	
cgc aaa aac att cga acc aaa caa caa att gct gag caa gta gcc aaa	528
Arg Lys Asn Ile Arg Thr Lys Gln Gln Ile Ala Glu Gln Val Ala Lys	
160 165 170	
gga act aaa gaa gct aaa gaa aaa ggt tta gct caa gtg gcc cat ctc	576
Gly Thr Lys Glu Ala Lys Glu Lys Gly Leu Ala Gln Val Ala His Leu	
175 180 185	
agt aaa gaa gaa gtt gcg gca gtc aat gaa gca aaa aga caa gga cgc	624
Ser Lys Glu Glu Val Ala Ala Val Asn Glu Ala Lys Arg Gln Gly Arg	
190 195 200	
tat act aca gac gat ggc tat att ttt agt ccg aca gat atc att gat	672
Tyr Thr Thr Asp Asp Gly Tyr Ile Phe Ser Pro Thr Asp Ile Ile Asp	
205 210 215 220	
gat tta gga gat gct tat tta gta cct cat ggt aat cac tat cat tat	720
Asp Leu Gly Asp Ala Tyr Leu Val Pro His Gly Asn His Tyr His Tyr	
225 230 235	
att cct aaa aag gat ttg tct cca agt gag cta gct gct gca caa gcc	768
Ile Pro Lys Lys Asp Leu Ser Pro Ser Glu Leu Ala Ala Ala Gln Ala	
240 245 250	
tac tgg agt caa aaa caa ggt cga ggt gct aga ccg tct gat tac cgc	816
Tyr Trp Ser Gln Lys Gln Gly Arg Gly Ala Arg Pro Ser Asp Tyr Arg	
255 260 265	
ccg aca cca gcc cca ggt cgt agg aaa gcc cca att cct gat gtg acg	864
Pro Thr Pro Ala Pro Gly Arg Arg Lys Ala Pro Ile Pro Asp Val Thr	
270 275 280	
cct aac cct gga caa ggt cat cag cca gat aac ggt ggc tat cat cca	912
Pro Asn Pro Gly Gln Gly His Gln Pro Asp Asn Gly Gly Tyr His Pro	
285 290 295 300	
gcg cct cct agg cca aat gat gcg tca caa aac aaa cac caa aga gat	960
Ala Pro Pro Arg Pro Asn Asp Ala Ser Gln Asn Lys His Gln Arg Asp	
305 310 315	
gag ttt aaa gga aaa acc ttt aag gaa ctt tta gat caa cta cac cgt	1008
Glu Phe Lys Gly Lys Thr Phe Lys Glu Leu Leu Asp Gln Leu His Arg	
320 325 330	
ctt gat ttg aaa tac cgt cat gtg gaa gaa gat ggg ttg att ttt gaa	1056
Leu Asp Leu Lys Tyr Arg His Val Glu Glu Asp Gly Leu Ile Phe Glu	
335 340 345	
ccg act caa gtg atc aaa tca aac gct ttt ggg tat gtg gtg cct cat	1104
Pro Thr Gln Val Ile Lys Ser Asn Ala Phe Gly Tyr Val Val Pro His	
350 355 360	

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gga gat cat tat cat att atc cca aga agt cag tta tca cct ctt gaa Gly Asp His Tyr His Ile Ile Pro Arg Ser Gln Leu Ser Pro Leu Glu 365 370 375 380	1152
atg gaa tta gca gat cga tac tta gct ggc caa act gag gac aat gac Met Glu Leu Ala Asp Arg Tyr Leu Ala Gly Gln Thr Glu Asp Asn Asp 385 390 395	1200
tca ggt tca gag cac tca aaa cca tca gat aaa gaa gtg aca cat acc Ser Gly Ser Glu His Ser Lys Pro Ser Asp Lys Glu Val Thr His Thr 400 405 410	1248
ttt ctt ggt cat cgc atc aaa gct tac gga aaa ggc tta gat ggt aaa Phe Leu Gly His Arg Ile Lys Ala Tyr Gly Lys Gly Leu Asp Gly Lys 415 420 425	1296
cca tat gat acg agt gat gct tat gtt ttt agt aaa gaa tcc att cat Pro Tyr Asp Thr Ser Asp Ala Tyr Val Phe Ser Lys Glu Ser Ile His 430 435 440	1344
tca gtg gat aaa tca gga gtt aca gct aaa cac gga gat cat ttc cac Ser Val Asp Lys Ser Gly Val Thr Ala Lys His Gly Asp His Phe His 445 450 455 460	1392
tat ata gga ttt gga gaa ctt gaa caa tat gag ttg gat gag gtc gct Tyr Ile Gly Phe Gly Glu Leu Glu Gln Tyr Glu Leu Asp Glu Val Ala 465 470 475	1440
aac tgg gtg aaa gca aaa ggt caa gct gat gag ctt gct gct gct ttg Asn Trp Val Lys Ala Lys Gly Gln Ala Asp Glu Leu Ala Ala Ala Leu 480 485 490	1488
gat cag gaa caa ggc aaa gaa aaa cca ctc ttt gac act aaa aaa gtg Asp Gln Glu Gln Gly Lys Glu Lys Pro Leu Phe Asp Thr Lys Lys Val 495 500 505	1536
agt cgc aaa gta aca aaa gat ggt aaa gtg ggc tat atg atg cca aaa Ser Arg Lys Val Thr Lys Asp Gly Lys Val Gly Tyr Met Met Pro Lys 510 515 520	1584
gat ggt aag gac tat ttc tat gct cgt gat caa ctt gat ttg act cag Asp Gly Lys Asp Tyr Phe Tyr Ala Arg Asp Gln Leu Asp Leu Thr Gln 525 530 535 540	1632
att gcc ttt gcc gaa caa gaa cta atg ctt aaa gat aag aag cat tac Ile Ala Phe Ala Glu Gln Glu Leu Met Leu Lys Asp Lys Lys His Tyr 545 550 555	1680
cgt tat gac att gtt gac aca ggt att gag cca cga ctt gct gta gat Arg Tyr Asp Ile Val Asp Thr Gly Ile Glu Pro Arg Leu Ala Val Asp 560 565 570	1728
gtg tca agt ctg ccg atg cat gct ggt aat gct act tac gat act gga Val Ser Ser Leu Pro Met His Ala Gly Asn Ala Thr Tyr Asp Thr Gly 575 580 585	1776

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agt tcg ttt gtt atc cca cat att gat cat atc cat gtc gtt ccg tat	1824
Ser Ser Phe Val Ile Pro His Ile Asp His Ile His Val Val Pro Tyr	
590 595 600	
tca tgg ttg acg cgc gat cag att gca aca gtc aag tat gtg atg caa	1872
Ser Trp Leu Thr Arg Asp Gln Ile Ala Thr Val Lys Tyr Val Met Gln	
605 610 615 620	
cac ccc gaa gtt cgt ccg gat gta tgg tct aag cca ggg cat gaa gag	1920
His Pro Glu Val Arg Pro Asp Val Trp Ser Lys Pro Gly His Glu Glu	
625 630 635	
tca ggt tcg gtc att cca aat gtt acg cct ctt gat aaa cgt gct ggt	1968
Ser Gly Ser Val Ile Pro Asn Val Thr Pro Leu Asp Lys Arg Ala Gly	
640 645 650	
atg cca aac tgg caa att atc cat tct gct gaa gaa gtt caa aaa gcc	2016
Met Pro Asn Trp Gln Ile Ile His Ser Ala Glu Glu Val Gln Lys Ala	
655 660 665	
cta gca gaa ggt cgt ttt gca aca cca gac ggc tat att ttc gat cca	2064
Leu Ala Glu Gly Arg Phe Ala Thr Pro Asp Gly Tyr Ile Phe Asp Pro	
670 675 680	
cga gat gtt ttg gcc aaa gaa act ttt gta tgg aaa gat ggc tcc ttt	2112
Arg Asp Val Leu Ala Lys Glu Thr Phe Val Trp Lys Asp Gly Ser Phe	
685 690 695 700	
agc atc cca aga gca gat ggc agt tca ttg aga acc att aat aaa tct	2160
Ser Ile Pro Arg Ala Asp Gly Ser Ser Leu Arg Thr Ile Asn Lys Ser	
705 710 715	
gat cta tcc caa gct gag tgg caa caa gct caa gag tta ttg gca aag	2208
Asp Leu Ser Gln Ala Glu Trp Gln Gln Ala Gln Glu Leu Leu Ala Lys	
720 725 730	
aaa aat act ggt gat gct act gat acg gat aaa ccc aaa gaa aag caa	2256
Lys Asn Thr Gly Asp Ala Thr Asp Thr Asp Lys Pro Lys Glu Lys Gln	
735 740 745	
cag gca gat aag agc aat gaa aac caa cag cca agt gaa gcc agt aaa	2304
Gln Ala Asp Lys Ser Asn Glu Asn Gln Gln Pro Ser Glu Ala Ser Lys	
750 755 760	
gaa gaa aaa gaa tca gat gac ttt ata gac agt tta cca gac tat ggt	2352
Glu Glu Lys Glu Ser Asp Asp Phe Ile Asp Ser Leu Pro Asp Tyr Gly	
765 770 775 780	
cta gat aga gca acc cta gaa gat cat atc aat caa tta gca caa aaa	2400
Leu Asp Arg Ala Thr Leu Glu Asp His Ile Asn Gln Leu Ala Gln Lys	
785 790 795	
gct aat atc gat cct aag tat ctc att ttc caa cca gaa ggt gtc caa	2448
Ala Asn Ile Asp Pro Lys Tyr Leu Ile Phe Gln Pro Glu Gly Val Gln	
800 805 810	



ttt tat aat aaa aat ggt gaa ttg gta act tat gat atc aag aca ctt 2496  
Phe Tyr Asn Lys Asn Gly Glu Leu Val Thr Tyr Asp Ile Lys Thr Leu  
815 820 825

caa caa ata aac cct taacccaaaag aagatctcat tggttaaagca ctgctttgtc 2551  
Gln Gln Ile Asn Pro  
830

aaagcaagtt	acggtgattt	tgaagtcatt	ctatgtaacg	agtagtgata	aaagttggat	2611
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gattcttgga	ctaattgtcaa	ataagtagac	agaaaactgt	gttattttattg	cgt	2726
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tcagccagcg	acacatcttt	gaaatgctgt	atttatctct	atttagcgtg	attattttccc	5171
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<210> 14

<211> 40

<212> PRT

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&lt;213&gt; Streptococcus

&lt;400&gt; 14

Phe	Gly	Ser	Ala	Leu	Ser	Thr	Val	Glu	Val	Lys	Glu	Ile	Ile	Ser	Glu
1				5					10					15	
Glu	Asn	Ile	Trp	Leu	Tyr	Arg	Leu	Ser	Cys	Cys	His	Phe	Thr	Ser	Tyr
			20					25					30		
Ser	Tyr	Trp	Lys	Leu	Pro	Thr	Trp								
		35					40								

&lt;210&gt; 15

&lt;211&gt; 793

&lt;212&gt; PRT

&lt;213&gt; Streptococcus

&lt;400&gt; 15

Met	Gly	Leu	Ala	Thr	Lys	Asp	Asn	Gln	Ile	Ala	Tyr	Ile	Asp	Asp	Ser
1				5					10					15	
Lys	Gly	Lys	Ala	Lys	Ala	Pro	Lys	Thr	Asn	Lys	Thr	Met	Asp	Gln	Ile
			20					25					30		
Ser	Ala	Glu	Glu	Gly	Ile	Ser	Ala	Glu	Gln	Ile	Val	Val	Lys	Ile	Thr
		35					40				45				
Asp	Gln	Gly	Tyr	Val	Thr	Ser	His	Gly	Asp	His	Tyr	His	Phe	Tyr	Asn
	50				55					60					
Gly	Lys	Val	Pro	Tyr	Asp	Ala	Ile	Ile	Ser	Glu	Glu	Leu	Leu	Met	Thr
65					70				75					80	
Asp	Pro	Asn	Tyr	Arg	Phe	Lys	Gln	Ser	Asp	Val	Ile	Asn	Glu	Ile	Leu
				85				90					95		
Asp	Gly	Tyr	Val	Ile	Lys	Val	Asn	Gly	Asn	Tyr	Tyr	Val	Tyr	Leu	Lys
			100					105					110		
Pro	Gly	Ser	Lys	Arg	Lys	Asn	Ile	Arg	Thr	Lys	Gln	Gln	Ile	Ala	Glu
		115					120					125			
Gln	Val	Ala	Lys	Gly	Thr	Lys	Glu	Ala	Lys	Glu	Lys	Gly	Leu	Ala	Gln
		130				135					140				
Val	Ala	His	Leu	Ser	Lys	Glu	Glu	Val	Ala	Ala	Val	Asn	Glu	Ala	Lys
145					150				155					160	
Arg	Gln	Gly	Arg	Tyr	Thr	Thr	Asp	Asp	Gly	Tyr	Ile	Phe	Ser	Pro	Thr
			165					170					175		
Asp	Ile	Ile	Asp	Asp	Leu	Gly	Asp	Ala	Tyr	Leu	Val	Pro	His	Gly	Asn
			180				185					190			
His	Tyr	His	Tyr	Ile	Pro	Lys	Lys	Asp	Leu	Ser	Pro	Ser	Glu	Leu	Ala
		195					200					205			
Ala	Ala	Gln	Ala	Tyr	Trp	Ser	Gln	Lys	Gln	Gly	Arg	Gly	Ala	Arg	Pro
		210				215					220				
Ser	Asp	Tyr	Arg	Pro	Thr	Pro	Ala	Pro	Gly	Arg	Arg	Lys	Ala	Pro	Ile
225					230				235					240	
Pro	Asp	Val	Thr	Pro	Asn	Pro	Gly	Gln	Gly	His	Gln	Pro	Asp	Asn	Gly
			245					250					255		
Gly	Tyr	His	Pro	Ala	Pro	Pro	Arg	Pro	Asn	Asp	Ala	Ser	Gln	Asn	Lys
		260					265					270			
His	Gln	Arg	Asp	Glu	Phe	Lys	Gly	Lys	Thr	Phe	Lys	Glu	Leu	Leu	Asp
		275					280				285				
Gln	Leu	His	Arg	Leu	Asp	Leu	Lys	Tyr	Arg	His	Val	Glu	Glu	Asp	Gly
	290					295				300					
Leu	Ile	Phe	Glu	Pro	Thr	Gln	Val	Ile	Lys	Ser	Asn	Ala	Phe	Gly	Tyr
305					310					315					320

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Val	Val	Pro	His	Gly	Asp	His	Tyr	His	Ile	Ile	Pro	Arg	Ser	Gln	Leu
				325					330					335	
Ser	Pro	Leu	Glu	Met	Glu	Leu	Ala	Asp	Arg	Tyr	Leu	Ala	Gly	Gln	Thr
			340					345					350		
Glu	Asp	Asn	Asp	Ser	Gly	Ser	Glu	His	Ser	Lys	Pro	Ser	Asp	Lys	Glu
		355					360					365			
Val	Thr	His	Thr	Phe	Leu	Gly	His	Arg	Ile	Lys	Ala	Tyr	Gly	Lys	Gly
	370					375					380				
Leu	Asp	Gly	Lys	Pro	Tyr	Asp	Thr	Ser	Asp	Ala	Tyr	Val	Phe	Ser	Lys
385					390					395					400
Glu	Ser	Ile	His	Ser	Val	Asp	Lys	Ser	Gly	Val	Thr	Ala	Lys	His	Gly
				405					410					415	
Asp	His	Phe	His	Tyr	Ile	Gly	Phe	Gly	Glu	Leu	Glu	Gln	Tyr	Glu	Leu
		420						425					430		
Asp	Glu	Val	Ala	Asn	Trp	Val	Lys	Ala	Lys	Gly	Gln	Ala	Asp	Glu	Leu
		435					440					445			
Ala	Ala	Ala	Leu	Asp	Gln	Glu	Gln	Gly	Lys	Glu	Lys	Pro	Leu	Phe	Asp
	450					455					460				
Thr	Lys	Lys	Val	Ser	Arg	Lys	Val	Thr	Lys	Asp	Gly	Lys	Val	Gly	Tyr
465					470					475					480
Met	Met	Pro	Lys	Asp	Gly	Lys	Asp	Tyr	Phe	Tyr	Ala	Arg	Asp	Gln	Leu
				485					490					495	
Asp	Leu	Thr	Gln	Ile	Ala	Phe	Ala	Glu	Gln	Glu	Leu	Met	Leu	Lys	Asp
			500					505					510		
Lys	Lys	His	Tyr	Arg	Tyr	Asp	Ile	Val	Asp	Thr	Gly	Ile	Glu	Pro	Arg
		515					520					525			
Leu	Ala	Val	Asp	Val	Ser	Ser	Leu	Pro	Met	His	Ala	Gly	Asn	Ala	Thr
	530						535				540				
Tyr	Asp	Thr	Gly	Ser	Ser	Phe	Val	Ile	Pro	His	Ile	Asp	His	Ile	His
545					550					555					560
Val	Val	Pro	Tyr	Ser	Trp	Leu	Thr	Arg	Asp	Gln	Ile	Ala	Thr	Val	Lys
				565					570					575	
Tyr	Val	Met	Gln	His	Pro	Glu	Val	Arg	Pro	Asp	Val	Trp	Ser	Lys	Pro
			580					585					590		
Gly	His	Glu	Glu	Ser	Gly	Ser	Val	Ile	Pro	Asn	Val	Thr	Pro	Leu	Asp
	595						600					605			
Lys	Arg	Ala	Gly	Met	Pro	Asn	Trp	Gln	Ile	Ile	His	Ser	Ala	Glu	Glu
	610					615					620				
Val	Gln	Lys	Ala	Leu	Ala	Glu	Gly	Arg	Phe	Ala	Thr	Pro	Asp	Gly	Tyr
625					630					635					640
Ile	Phe	Asp	Pro	Arg	Asp	Val	Leu	Ala	Lys	Glu	Thr	Phe	Val	Trp	Lys
				645					650					655	
Asp	Gly	Ser	Phe	Ser	Ile	Pro	Arg	Ala	Asp	Gly	Ser	Ser	Leu	Arg	Thr
			660					665					670		
Ile	Asn	Lys	Ser	Asp	Leu	Ser	Gln	Ala	Glu	Trp	Gln	Gln	Ala	Gln	Glu
	675						680					685			
Leu	Leu	Ala	Lys	Lys	Asn	Thr	Gly	Asp	Ala	Thr	Asp	Thr	Asp	Lys	Pro
	690					695					700				
Lys	Glu	Lys	Gln	Gln	Ala	Asp	Lys	Ser	Asn	Glu	Asn	Gln	Gln	Pro	Ser
705					710					715					720
Glu	Ala	Ser	Lys	Glu	Glu	Lys	Glu	Ser	Asp	Asp	Phe	Ile	Asp	Ser	Leu
				725					730					735	
Pro	Asp	Tyr	Gly	Leu	Asp	Arg	Ala	Thr	Leu	Glu	Asp	His	Ile	Asn	Gln
			740					745					750		
Leu	Ala	Gln	Lys	Ala	Asn	Ile	Asp	Pro	Lys	Tyr	Leu	Ile	Phe	Gln	Pro
	755						760					765			

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Glu Gly Val Gln Phe Tyr Asn Lys Asn Gly Glu Leu Val Thr Tyr Asp  
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 Ile Lys Thr Leu Gln Gln Ile Asn Pro  
 785 790

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 <212> PRT  
 <213> Streptococcus

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 Leu Lys Pro Gly Ser Lys Arg Lys Asn Ile Arg Thr Lys Gln Gln Ile  
 35 40 45  
 Ala Glu Gln Val Ala Lys Gly Thr Lys Glu Ala Lys Glu Lys Gly Leu  
 50 55 60  
 Ala Gln Val Ala His Leu Ser Lys Glu Glu Val Ala Ala Val Asn Glu  
 65 70 75 80  
 Ala Lys Arg Gln Gly Arg Tyr Thr Thr Asp Asp Gly Tyr Ile Phe Ser  
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 Pro Thr Asp Ile Ile Asp Asp Leu Gly Asp Ala Tyr Leu Val Pro His  
 100 105 110  
 Gly Asn His Tyr His Tyr Ile Pro Lys Lys Asp Leu Ser Pro Ser Glu  
 115 120 125  
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 130 135 140  
 Arg Pro Ser Asp Tyr Arg Pro Thr Pro Ala Pro Gly Arg Arg Lys Ala  
 145 150 155 160  
 Pro Ile Pro Asp Val Thr Pro Asn Pro Gly Gln Gly His Gln Pro Asp  
 165 170 175  
 Asn Gly Gly Tyr His Pro Ala Pro Pro Arg Pro Asn Asp Ala Ser Gln  
 180 185 190  
 Asn Lys His Gln Arg Asp Glu Phe Lys Gly Lys Thr Phe Lys Glu Leu  
 195 200 205  
 Leu Asp Gln Leu His Arg Leu Asp Leu Lys Tyr Arg His Val Glu Glu  
 210 215 220  
 Asp Gly Leu Ile Phe Glu Pro Thr Gln Val Ile Lys Ser Asn Ala Phe  
 225 230 235 240  
 Gly Tyr Val Val Pro His Gly Asp His Tyr His Ile Ile Pro Arg Ser  
 245 250 255  
 Gln Leu Ser Pro Leu Glu Met Glu Leu Ala Asp Arg Tyr Leu Ala Gly  
 260 265 270  
 Gln Thr Glu Asp Asn Asp Ser Gly Ser Glu His Ser Lys Pro Ser Asp  
 275 280 285  
 Lys Glu Val Thr His Thr Phe Leu Gly His Arg Ile Lys Ala Tyr Gly  
 290 295 300  
 Lys Gly Leu Asp Gly Lys Pro Tyr Asp Thr Ser Asp Ala Tyr Val Phe  
 305 310 315 320  
 Ser Lys Glu Ser Ile His Ser Val Asp Lys Ser Gly Val Thr Ala Lys  
 325 330 335  
 His Gly Asp His Phe His Tyr Ile Gly Phe Gly Glu Leu Glu Gln Tyr  
 340 345 350

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Glu Leu Asp Glu Val Ala Asn Trp Val Lys Ala Lys Gly Gln Ala Asp  
 355 360 365  
 Glu Leu Ala Ala Ala Leu Asp Gln Glu Gln Gly Lys Glu Lys Pro Leu  
 370 375 380  
 Phe Asp Thr Lys Lys Val Ser Arg Lys Val Thr Lys Asp Gly Lys Val  
 385 390 395 400  
 Gly Tyr Met Met Pro Lys Asp Gly Lys Asp Tyr Phe Tyr Ala Arg Asp  
 405 410 415  
 Gln Leu Asp Leu Thr Gln Ile Ala Phe Ala Glu Gln Glu Leu Met Leu  
 420 425 430  
 Lys Asp Lys Lys His Tyr Arg Tyr Asp Ile Val Asp Thr Gly Ile Glu  
 435 440 445  
 Pro Arg Leu Ala Val Asp Val Ser Ser Leu Pro Met His Ala Gly Asn  
 450 455 460  
 Ala Thr Tyr Asp Thr Gly Ser Ser Phe Val Ile Pro His Ile Asp His  
 465 470 475 480  
 Ile His Val Val Pro Tyr Ser Trp Leu Thr Arg Asp Gln Ile Ala Thr  
 485 490 495  
 Val Lys Tyr Val Met Gln His Pro Glu Val Arg Pro Asp Val Trp Ser  
 500 505 510  
 Lys Pro Gly His Glu Glu Ser Gly Ser Val Ile Pro Asn Val Thr Pro  
 515 520 525  
 Leu Asp Lys Arg Ala Gly Met Pro Asn Trp Gln Ile His Ser Ala  
 530 535 540  
 Glu Glu Val Gln Lys Ala Leu Ala Glu Gly Arg Phe Ala Thr Pro Asp  
 545 550 555 560  
 Gly Tyr Ile Phe Asp Pro Arg Asp Val Leu Ala Lys Glu Thr Phe Val  
 565 570 575  
 Trp Lys Asp Gly Ser Phe Ser Ile Pro Arg Ala Asp Gly Ser Ser Leu  
 580 585 590  
 Arg Thr Ile Asn Lys Ser Asp Leu Ser Gln Ala Glu Trp Gln Gln Ala  
 595 600 605  
 Gln Glu Leu Leu Ala Lys Lys Asn Thr Gly Asp Ala Thr Asp Thr Asp  
 610 615 620  
 Lys Pro Lys Glu Lys Gln Gln Ala Asp Lys Ser Asn Glu Asn Gln Gln  
 625 630 635 640  
 Pro Ser Glu Ala Ser Lys Glu Glu Lys Glu Ser Asp Asp Phe Ile Asp  
 645 650 655  
 Ser Leu Pro Asp Tyr Gly Leu Asp Arg Ala Thr Leu Glu Asp His Ile  
 660 665 670  
 Asn Gln Leu Ala Gln Lys Ala Asn Ile Asp Pro Lys Tyr Leu Ile Phe  
 675 680 685  
 Gln Pro Glu Gly Val Gln Phe Tyr Asn Lys Asn Gly Glu Leu Val Thr  
 690 695 700  
 Tyr Asp Ile Lys Thr Leu Gln Gln Ile Asn Pro  
 705 710 715

&lt;210&gt; 17

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Streptococcus

&lt;400&gt; 17

Met His Ser Phe Ser Asn Pro Gly Tyr Pro Tyr Asp Asn Ala Val Thr  
 1 5 10 15

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Glu Ala Phe Phe Lys Tyr Leu Lys His Arg Gln Ile Asn Arg Lys His  
                   20                  25                  30  
 Tyr Gln Asn Ile Lys Gln Val Gln Leu Asp Cys Phe Glu Tyr Ile Glu  
                   35                  40                  45  
 Asn Phe Tyr Asn Asn Tyr Asn Pro His Thr Ala Asn Leu Gly Leu Thr  
           50                  55                  60  
 Pro Asn Gln Lys Glu Glu Asn Tyr Phe Asn Ala Ile Lys  
 65                  70                  75

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 <213> Streptococcus

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 Ser Arg Lys Gly Thr Pro Ala Asp Asn Ala Cys Ile Glu Trp Phe His  
           20                  25                  30  
 Thr Val Leu Lys Thr Glu Thr Phe Tyr Phe His Asn Arg Arg Lys Tyr  
           35                  40                  45  
 Asn Lys Asp Ser Ile Thr Asn Ile Val Lys Asn Tyr Ile Thr Phe Tyr  
           50                  55                  60  
 Asn Glu Thr Arg Ile Gln Gln Arg Leu Asn Asp Gln Ser Pro Val Gln  
 65                  70                  75                  80  
 Tyr Arg Lys Leu Ile Ala  
                   85

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 <211> 126  
 <212> PRT  
 <213> Streptococcus

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           20                  25                  30  
 Met Lys Asn Asn Gly Trp Leu Cys Arg Thr Arg Thr Lys Lys Val Pro  
           35                  40                  45  
 Asn Leu Gly Lys Ala Tyr Tyr Leu Thr Asp Asn Lys Leu Ser Arg Asp  
           50                  55                  60  
 Phe His Ala Asp Lys Pro Lys Glu Lys Leu Val Thr Asp Ile Thr Tyr  
 65                  70                  75                  80  
 Leu Tyr Phe Gly Asn Cys Lys Leu Tyr Leu Ser Ser Ile Met Asn Leu  
                   85                  90                  95  
 Tyr Asn Arg Glu Ile Ile Ala Tyr Thr Ile Ser Asp Cys Gln Asp Thr  
           100                  105                  110  
 Asp Phe Val Leu Asp Thr Leu Asn Gln Leu Lys Leu Pro Lys  
           115                  120                  125

<210> 20  
 <211> 96  
 <212> PRT  
 <213> Streptococcus

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      20          25          30
Ile Lys Asn Asn Ser Gln Ile Tyr Thr Trp Met Lys Trp Tyr Glu Asn
      35          40          45
Glu Glu Leu Tyr Arg Phe His Gln Gly Val Gly Lys Gln Tyr Thr Tyr
      50          55          60
Gly Lys Gly Leu Glu His Leu Ser Glu Val Glu Gln Leu Gln Leu Gln
65          70          75          80
Val Asp Leu Leu Lys Lys Tyr Arg Gly Leu Ile Arg Lys Ser Ile Lys
      85          90          95

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      <210> 21
      <211> 288
      <212> PRT
      <213> streptococcus

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Ile Ile Thr Ala Asn Lys Asp Lys Tyr Ser Ile Ser Lys Met Cys Arg
      20          25          30
Trp Leu Asn Met Pro His Ser Ser Tyr Tyr Tyr Gln Ala Val Glu Ser
      35          40          45
Val Ser Glu Thr Glu Phe Glu Glu Thr Ile Lys Arg Ile Phe Leu Asp
      50          55          60
Ser Glu Ser Arg Tyr Gly Ser Arg Lys Ile Lys Ile Cys Leu Asn Asn
65          70          75          80
Glu Gly Ile Thr Leu Ser Arg Arg Arg Ile Arg Arg Ile Met Lys Arg
      85          90          95
Leu Asn Leu Val Ser Val Tyr Gln Lys Ala Thr Phe Lys Pro His Ser
      100          105          110
Arg Gly Lys Asn Glu Ala Pro Ile Pro Asn His Leu Asp Arg Gln Phe
      115          120          125
Lys Gln Glu Arg Pro Leu Gln Ala Leu Val Thr Asp Leu Thr Tyr Val
      130          135          140
Arg Val Gly Asn Arg Trp Ala Tyr Val Cys Leu Ile Ile Asp Leu Tyr
145          150          155          160
Asn Arg Glu Ile Ile Gly Leu Ser Leu Gly Trp His Lys Thr Ala Glu
      165          170          175
Leu Val Lys Gln Ala Ile Gln Ser Ile Pro Tyr Ala Leu Thr Lys Val
      180          185          190
Lys Met Phe His Ser Asp Arg Gly Lys Glu Phe Asp Asn Gln Leu Ile
      195          200          205
Asp Glu Ile Leu Glu Ala Phe Gly Ile Thr Arg Ser Leu Ser Gln Ala
      210          215          220
Gly Tyr Pro Tyr Asp Asn Ala Val Ala Glu Ser Thr Tyr Arg Ala Phe
225          230          235          240
Lys Ile Glu Phe Val Tyr Gln Glu Thr Phe Gln Leu Leu Glu Glu Leu
      245          250          255
Ala Leu Lys Thr Lys Asp Tyr Val His Trp Trp Asn Tyr His Arg Ile
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His Gly Ser Leu Asn Tyr Gln Thr Pro Met Thr Lys Arg Leu Ile Ala
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<220>
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ggt tat ggt aaa tct gct cat ggt tca aca cca caa gaa ggt gtt aat      96
Val Tyr Gly Lys Ser Ala His Gly Ser Thr Pro Gln Glu Gly Val Asn
              20              25              30

ggg gcg act tat tta gct ctt tat cta agt caa ttt gat ttt gaa ggt      144
Gly Ala Thr Tyr Leu Ala Leu Tyr Leu Ser Gln Phe Asp Phe Glu Gly
              35              40              45

cct gct cgt gct ttc tta gat gtt aca gcc aac att att cac gaa gac      192
Pro Ala Arg Ala Phe Leu Asp Val Thr Ala Asn Ile Ile His Glu Asp
              50              55              60

ttc tca ggt gaa aaa ctt gga gta gct tat gaa gat gac tgt atg gga      240
Phe Ser Gly Glu Lys Leu Gly Val Ala Tyr Glu Asp Asp Cys Met Gly
              65              70              75              80

cca ttg agc atg aat gca ggt gtc ttc cag ttt gat gaa act aat gat      288
Pro Leu Ser Met Asn Ala Gly Val Phe Gln Phe Asp Glu Thr Asn Asp
              85              90              95

gat aat act atc gct ctt aat ttc cgt tac cca caa ggg aca gat gct      336
Asp Asn Thr Ile Ala Leu Asn Phe Arg Tyr Pro Gln Gly Thr Asp Ala
              100              105              110

aaa act atc caa act aag ctt gag aaa ctt aac gga gtt gaa aaa gtg      384
Lys Thr Ile Gln Thr Lys Leu Glu Lys Leu Asn Gly Val Glu Lys Val
              115              120              125

act ctt tct gac cat gaa cac aca cca cac tat gta cct atg gac gat      432
Thr Leu Ser Asp His Glu His Thr Pro His Tyr Val Pro Met Asp Asp
              130              135              140

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gaa tta gta tca acc tta cta gct gtc tat gaa aag caa act ggt ctt	480
Glu Leu Val Ser Thr Leu Leu Ala Val Tyr Glu Lys Gln Thr Gly Leu	
145 150 155 160	
aaa gga cat gaa cag gtt att ggt ggt ggg aca ttt ggt cgc tta ctt	528
Lys Gly His Glu Gln Val Ile Gly Gly Gly Thr Phe Gly Arg Leu Leu	
165 170 175	
gaa cgg ggt gtt gca tac ggt gcc atg ttc cca gga gat gaa aac act	576
Glu Arg Gly Val Ala Tyr Gly Ala Met Phe Pro Gly Asp Glu Asn Thr	
180 185 190	
atg cat caa gct aat gag tac atg cct tta gaa aat att ttc cgt tcg	624
Met His Gln Ala Asn Glu Tyr Met Pro Leu Glu Asn Ile Phe Arg Ser	
195 200 205	
gct gct atc tac gca gaa gct atc tat gaa tta atc aaa taaaataatc	673
Ala Ala Ile Tyr Ala Glu Ala Ile Tyr Glu Leu Ile Lys	
210 215 220	
cttaactaa atatgtgatac aatgataaag ggtggtgaag acatgaaagt gtctttgcct	733
cttttcataa ggtagatttt ggagacttt atg act gac ttg gaa aaa att att	786
Met Thr Asp Leu Glu Lys Ile Ile	
225	
aaa gca ata aaa agt gat tca cag aat caa aat tat aca gaa aat ggt	834
Lys Ala Ile Lys Ser Asp Ser Gln Asn Gln Asn Tyr Thr Glu Asn Gly	
230 235 240 245	
att gat cct ttg ttt gct gct cct aaa aca gct agg atc aat att gtt	882
Ile Asp Pro Leu Phe Ala Ala Pro Lys Thr Ala Arg Ile Asn Ile Val	
250 255 260	
ggc caa gca cct ggt tta aaa act caa gaa gca aga ctc tat tgg aaa	930
Gly Gln Ala Pro Gly Leu Lys Thr Gln Glu Ala Arg Leu Tyr Trp Lys	
265 270 275	
gat aaa tct gga gat cgt cta cgc cag tgg ctt gga gtt gat gaa gag	978
Asp Lys Ser Gly Asp Arg Leu Arg Gln Trp Leu Gly Val Asp Glu Glu	
280 285 290	
aca ttt tac cat tct gga aaa ttt gct gtt tta cct tta gat ttt tat	1026
Thr Phe Tyr His Ser Gly Lys Phe Ala Val Leu Pro Leu Asp Phe Tyr	
295 300 305	
tac cca ggc aaa gga aaa tca gga gat tta ccc cct aga aaa ggt ttt	1074
Tyr Pro Gly Lys Gly Lys Ser Gly Asp Leu Pro Pro Arg Lys Gly Phe	
310 315 320 325	
gcg gag aaa tgg cac cct ctt att tta aaa gaa atg cct aat gtt caa	1122
Ala Glu Lys Trp His Pro Leu Ile Leu Lys Glu Met Pro Asn Val Gln	
330 335 340	
ttg acc ttg cta gtt ggt cag tat gct cag aaa tat tat ctt gga agc	1170
Leu Thr Leu Leu Val Gly Gln Tyr Ala Gln Lys Tyr Tyr Leu Gly Ser	
345 350 355	

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tcc gca cat aaa aat cta aca gaa aca gtt aaa gct tac aaa gac tat	1218
Ser Ala His Lys Asn Leu Thr Glu Thr Val Lys Ala Tyr Lys Asp Tyr	
360 365 370	
cta ccc gat tat tta ccc ctg gtt cac cca tca ccg cga aat caa att	1266
Leu Pro Asp Tyr Leu Pro Leu Val His Pro Ser Pro Arg Asn Gln Ile	
375 380 385	
tgg cta aag aag aat cca tgg ttt gaa aaa gat cta atc gtt gat tta	1314
Trp Leu Lys Lys Asn Pro Trp Phe Glu Lys Asp Leu Ile Val Asp Leu	
390 395 400 405	
caa aag ata gta gca gat att tta aaa gat taaggatagg agttgggt atg	1364
Gln Lys Ile Val Ala Asp Ile Leu Lys Asp Met	
410 415	
aga gat aat cat cta cac acg tat ttt tcc tat gat tgt caa acg gca	1412
Arg Asp Asn His Leu His Thr Tyr Phe Ser Tyr Asp Cys Gln Thr Ala	
420 425 430	
ttt gag gac tat att aat ggt ttt aca ggt gaa ttt atc acg aca gaa	1460
Phe Glu Asp Tyr Ile Asn Gly Phe Thr Gly Glu Phe Ile Thr Thr Glu	
435 440 445	
cat ttt gat tta tca aat cct tac acc ggt caa gac gat gtt cct gat	1508
His Phe Asp Leu Ser Asn Pro Tyr Thr Gly Gln Asp Asp Val Pro Asp	
450 455 460	
tat agt gct tat tgt caa aaa ata gat tat ctt aat cag aaa tat gga	1556
Tyr Ser Ala Tyr Cys Gln Lys Ile Asp Tyr Leu Asn Gln Lys Tyr Gly	
465 470 475 480	
aat cga ttt aaa aaa gga att gaa atc ggt tat ttt aaa gat agg gaa	1604
Asn Arg Phe Lys Lys Gly Ile Glu Ile Gly Tyr Phe Lys Asp Arg Glu	
485 490 495	
tca gat att tta gat tat tta aaa aat aaa gaa ttt gat tta aaa cta	1652
Ser Asp Ile Leu Asp Tyr Leu Lys Asn Lys Glu Phe Asp Leu Lys Leu	
500 505 510	
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Leu Ser Ile His His Asn Gly Arg Tyr Asp Tyr Leu Gln Glu Glu Ala	
515 520 525	
ctg aaa gta cca aca aag gga gct ttt agc aga tta ctt taatcgtatg	1749
Leu Lys Val Pro Thr Lys Gly Ala Phe Ser Arg Leu Leu	
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aagttaaact tagatgtaga agatttaaaa ccgttttgaaa cgcaattgaa gcgcattttc	1869
ataaagatgt tatctaagggt gtttagctttt gaactaaata ccaaattccct ttatctatat	1929
gggaatgaaa aacttttatcg ctatgcttta gagatactca aacagcttgg ttgtaaacaa	1989
tactctatag gctctgacgg tcatattcct gaacattttt gttatgaatt tgatagactt	2049
caaggtctgc taaaggacta tcaaattgat gaaaatcatt tgatatgagg aaatttttga	2109
taaaaaagct aggcaatatt gcttagcttt tttgtaatgc tattgatagt tttagtgaaa	2169

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atttcaaaaa	aataaagaaa	tcatttactt	gttgcaagcg	cttgcgtaaa	ttggttatgat	2229
tttattggta	acaattcatt	aaaaaaggag	aatgat	atg	aaa aga aaa gac tta	2283
			Met	Lys	Arg Lys Asp Leu	
					545	
ttt ggt gat	aaa caa act	caa tac acg	att aga aag	tta agt gtt	gga	2331
Phe Gly Asp	Lys Gln Thr	Gln Tyr Thr	Ile Arg Lys	Leu Ser Val	Gly	
	550		555		560	
gta gct tca	gtt aca aca	ggg gta tgt	att ttt ctt	cat agt cca	cag	2379
Val Ala Ser	Val Thr Thr	Gly Val Cys	Ile Phe Leu	His Ser Pro	Gln	
	565		570		575	
gta ttt gct	gaa gaa gta	agt gtt tct	cct gca act	aca gcg att	gca	2427
Val Phe Ala	Glu Glu Val	Ser Val Ser	Pro Ala Thr	Thr Ala Ile	Ala	
	580		585		590 595	
gag tcg aat	att aat cag	gtt gac aac	caa caa tct	act aat tta	aaa	2475
Glu Ser Asn	Ile Asn Gln	Val Asp Asn	Gln Gln Ser	Thr Asn Leu	Lys	
	600		605		610	
gat gac ata	aac tca aac	tct gag acg	gtt gtg aca	ccc tca gat	atg	2523
Asp Asp Ile	Asn Ser Asn	Ser Glu Thr	Val Val Thr	Pro Ser Asp	Met	
	615		620		625	
ccg gat acc	aag caa tta	gta tca gat	gaa act gac	act caa aag	gga	2571
Pro Asp Thr	Lys Gln Leu	Val Ser Asp	Glu Thr Asp	Thr Gln Lys	Gly	
	630		635		640	
gtg aca gag	ccg gat aag	gcg aca agc	ctg ctt gaa	gaa aat aaa	ggg	2619
Val Thr Glu	Pro Asp Lys	Ala Thr Ser	Leu Leu Glu	Glu Asn Lys	Gly	
	645		650		655	
cct gtt tca	gat aaa aat	acc tta gat	tta aaa gta	gca cca tct	aca	2667
Pro Val Ser	Asp Lys Asn	Thr Leu Asp	Leu Lys Val	Ala Pro Ser	Thr	
	660		665		670 675	
ttg caa aat	act ccc gac	aaa act tct	caa gct ata	ggg gct cca	agc	2715
Leu Gln Asn	Thr Pro Asp	Lys Thr Ser	Gln Ala Ile	Gly Ala Pro	Ser	
	680		685		690	
cct acc ttg	aaa gta gct	aat caa gct	cca cgg att	gaa aat ggt	tac	2763
Pro Thr Leu	Lys Val Ala	Asn Gln Ala	Pro Arg Ile	Glu Asn Gly	Tyr	
	695		700		705	
ttt agg cta	cat ctt aaa	gaa ttg cct	caa ggt cat	cct gta gaa	agc	2811
Phe Arg Leu	His Leu Lys	Glu Leu Pro	Gln Gly His	Pro Val Glu	Ser	
	710		715		720	
act gga ctt	tgg ata tgg	gga gat gtt	gat caa ccg	tct agt aat	tgg	2859
Thr Gly Leu	Trp Ile Trp	Gly Asp Val	Asp Gln Pro	Ser Ser Asn	Trp	
	725		730		735	
cca aat ggt	gct atc cct	atg act gat	gct aag aaa	gat gat tac	ggg	2907
Pro Asn Gly	Ala Ile Pro	Met Thr Asp	Ala Lys Lys	Asp Asp Tyr	Gly	
	740		745		750 755	

tat tat gtt gat ttt aaa tta tct gaa aaa caa cga aaa caa ata tct	2955
Tyr Tyr Val Asp Phe Lys Leu Ser Glu Lys Gln Arg Lys Gln Ile Ser	
760 765 770	
ttt tta att aat aac aaa gca ggg aca aat tta agc ggc gat cat cat	3003
Phe Leu Ile Asn Asn Lys Ala Gly Thr Asn Leu Ser Gly Asp His His	
775 780 785	
att cca tta tta cga cct gag atg aac caa gtt tgg att gat gaa aag	3051
Ile Pro Leu Leu Arg Pro Glu Met Asn Gln Val Trp Ile Asp Glu Lys	
790 795 800	
tac ggt ata cat act tat caa ccc ctc aaa gaa ggg tat gtc cgt att	3099
Tyr Gly Ile His Thr Tyr Gln Pro Leu Lys Glu Gly Tyr Val Arg Ile	
805 810 815	
aac tat ttg agt tcc tct agt aac tat gac cac tta tca gca tgg ctc	3147
Asn Tyr Leu Ser Ser Ser Ser Asn Tyr Asp His Leu Ser Ala Trp Leu	
820 825 830 835	
ttt aaa gat gtt gca acc ccy tca aca act tgg cca gat ggt agt aat	3195
Phe Lys Asp Val Ala Thr Xaa Ser Thr Thr Trp Pro Asp Gly Ser Asn	
840 845 850	
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Phe Val Asn Gln Gly Leu Tyr Gly Arg Tyr Ile Asp Val Ser Leu Lys	
855 860 865	
act aac gcc aaa gag att ggt ttt cta atc tta gat gaa agt aag aca	3291
Thr Asn Ala Lys Glu Ile Gly Phe Leu Ile Leu Asp Glu Ser Lys Thr	
870 875 880	
gga gat gca gtg aaa gtt caa ccc aac gac tat gtt ttt aga gat tta	3339
Gly Asp Ala Val Lys Val Gln Pro Asn Asp Tyr Val Phe Arg Asp Leu	
885 890 895	
gct aac cat aac caa att ttt gta aaa gat aag gat cca aag gtt tat	3387
Ala Asn His Asn Gln Ile Phe Val Lys Asp Lys Asp Pro Lys Val Tyr	
900 905 910 915	
aat aat cct tat tac att gat caa gtg cag cta aag gat gcc caa caa	3435
Asn Asn Pro Tyr Tyr Ile Asp Gln Val Gln Leu Lys Asp Ala Gln Gln	
920 925 930	
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Ile Asp Leu Thr Ser Ile Gln Ala Ser Phe Thr Thr Leu Asp Gly Val	
935 940 945	
gat aaa act gaa att tta aaa gaa ttg aaa gtg act gat aaa aat caa	3531
Asp Lys Thr Glu Ile Leu Lys Glu Leu Lys Val Thr Asp Lys Asn Gln	
950 955 960	
aat gct ata caa att tct gat atc act ctc gat act agt aaa tct ctt	3579
Asn Ala Ile Gln Ile Ser Asp Ile Thr Leu Asp Thr Ser Lys Ser Leu	
965 970 975	

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Leu Ile Ile Lys Gly Asp Phe Asn Pro Lys Gln Gly His Phe Asn Ile	
980 985 990 995	
tct tat aat ggt aac aat gtc atg aca agg caa tct tgg gaa ttt aaa	3675
Ser Tyr Asn Gly Asn Asn Val Met Thr Arg Gln Ser Trp Glu Phe Lys	
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gac caa ctt tat gct tat agt gga aat tta ggt gca gtt ctc aat caa	3723
Asp Gln Leu Tyr Ala Tyr Ser Gly Asn Leu Gly Ala Val Leu Asn Gln	
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Asp Gly Ser Lys Val Glu Ala Ser Leu Trp Ser Pro Ser Ala Asp Ser	
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Val Thr Met Ile Ile Tyr Asp Lys Asp Asn Gln Asn Arg Val Val Ala	
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act acc ccc ctt gtg aaa aat aat aaa ggt gtt tgg cag acg ata ctt	3867
Thr Thr Pro Leu Val Lys Asn Asn Lys Gly Val Trp Gln Thr Ile Leu	
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Asp Thr Lys Leu Gly Ile Lys Asn Tyr Thr Gly Tyr Tyr Tyr Leu Tyr	
1080 1085 1090	
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Glu Ile Lys Arg Gly Lys Asp Lys Val Lys Ile Leu Asp Pro Tyr Ala	
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Lys Ser Leu Ala Glu Trp Asp Ser Asn Thr Val Asn Asp Asp Ile Lys	
1110 1115 1120	
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Thr Ala Lys Ala Ala Phe Val Asn Pro Ser Gln Leu Gly Pro Gln Asn	
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Leu Ser Phe Ala Lys Ile Ala Asn Phe Lys Gly Arg Gln Asp Ala Val	
1140 1145 1150 1155	
ata tac gaa gca cat gta aga gac ttc act tct gat cga tct ttg gat	4155
Ile Tyr Glu Ala His Val Arg Asp Phe Thr Ser Asp Arg Ser Leu Asp	
1160 1165 1170	
gga aaa tta aaa aat caa ttt ggt acc ttt gca gcc ttt tca gag aaa	4203
Gly Lys Leu Lys Asn Gln Phe Gly Thr Phe Ala Ala Phe Ser Glu Lys	
1175 1180 1185	
cta gat tat tta cag aaa tta gga gtt aca cac att cag ctt tta ccg	4251
Leu Asp Tyr Leu Gln Lys Leu Gly Val Thr His Ile Gln Leu Leu Pro	
1190 1195 1200	

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tca gca cgt atc gcc gaa tta aaa caa tta ata cat gat att cat aaa Ser Ala Arg Ile Ala Glu Leu Lys Gln Leu Ile His Asp Ile His Lys 1255 1260 1265	4443
cgt ggc atg ggg gtt ata ctt gat gtc gtc tat aat cac act gca aaa Arg Gly Met Gly Val Ile Leu Asp Val Val Tyr Asn His Thr Ala Lys 1270 1275 1280	4491
act tat ctc ttt gag gat ata gaa cct aat tat tat cac ttt atg aat Thr Tyr Leu Phe Glu Asp Ile Glu Pro Asn Tyr Tyr His Phe Met Asn 1285 1290 1295	4539
gaa gat ggt tca cca aga gaa agt ttt gga ggg gga cgt tta gga acc Glu Asp Gly Ser Pro Arg Glu Ser Phe Gly Gly Gly Arg Leu Gly Thr 1300 1305 1310 1315	4587
act cat gca atg agt cgt cgt gtt ttg gtt gat tcc att aaa tat ctt Thr His Ala Met Ser Arg Arg Val Leu Val Asp Ser Ile Lys Tyr Leu 1320 1325 1330	4635
aca agt gaa ttt aaa gtt gat ggt ttc cgt ttt gat atg atg gga gat Thr Ser Glu Phe Lys Val Asp Gly Phe Arg Phe Asp Met Met Gly Asp 1335 1340 1345	4683
cat gat gcg gct gcg att gaa tta gct tat aaa gaa gct aaa gct att His Asp Ala Ala Ile Glu Leu Ala Tyr Lys Glu Ala Lys Ala Ile 1350 1355 1360	4731
aat cct aat atg att atg att ggt gag ggc tgg aga aca ttc caa ggc Asn Pro Asn Met Ile Met Ile Gly Glu Gly Trp Arg Thr Phe Gln Gly 1365 1370 1375	4779
gat caa ggt cag ccg gtt aaa cca gct gac caa gat tgg atg aag tca Asp Gln Gly Gln Pro Val Lys Pro Ala Asp Gln Asp Trp Met Lys Ser 1380 1385 1390 1395	4827
acc gat aca gtt ggc gtc ttt tca gat gat att cgt aat agc ttg aaa Thr Asp Thr Val Gly Val Phe Ser Asp Asp Ile Arg Asn Ser Leu Lys 1400 1405 1410	4875
tct ggt ttt cca aat gaa ggt act cca gct ttc atc aca ggt ggc cca Ser Gly Phe Pro Asn Glu Gly Thr Pro Ala Phe Ile Thr Gly Gly Pro 1415 1420 1425	4923

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caa tct tta caa ggt att ttt aaa aat atc aaa gca caa cct ggg aat 4971  
 Gln Ser Leu Gln Gly Ile Phe Lys Asn Ile Lys Ala Gln Pro Gly Asn  
           1430                          1435                          1440

ttt gaa gca gat tcg cca gga gat gtg gtg cag tat att gct gca cat 5019  
 Phe Glu Ala Asp Ser Pro Gly Asp Val Val Gln Tyr Ile Ala Ala His  
           1445                          1450                          1455

gat aac ctt acc ttg cat gat gtg att gca aaa tca att 5058  
 Asp Asn Leu Thr Leu His Asp Val Ile Ala Lys Ser Ile  
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 <212> PRT  
 <213> streptococcus

<400> 23  
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 Val Tyr Gly Lys Ser Ala His Gly Ser Thr Pro Gln Glu Gly Val Asn  
           20                  25                  30  
 Gly Ala Thr Tyr Leu Ala Leu Tyr Leu Ser Gln Phe Asp Phe Glu Gly  
           35                  40                  45  
 Pro Ala Arg Ala Phe Leu Asp Val Thr Ala Asn Ile Ile His Glu Asp  
           50                  55                  60  
 Phe Ser Gly Glu Lys Leu Gly Val Ala Tyr Glu Asp Asp Cys Met Gly  
           65                  70                  75                  80  
 Pro Leu Ser Met Asn Ala Gly Val Phe Gln Phe Asp Glu Thr Asn Asp  
                   85                  90                  95  
 Asp Asn Thr Ile Ala Leu Asn Phe Arg Tyr Pro Gln Gly Thr Asp Ala  
           100                  105                  110  
 Lys Thr Ile Gln Thr Lys Leu Glu Lys Leu Asn Gly Val Glu Lys Val  
           115                  120                  125  
 Thr Leu Ser Asp His Glu His Thr Pro His Tyr Val Pro Met Asp Asp  
           130                  135                  140  
 Glu Leu Val Ser Thr Leu Leu Ala Val Tyr Glu Lys Gln Thr Gly Leu  
           145                  150                  155                  160  
 Lys Gly His Glu Gln Val Ile Gly Gly Gly Thr Phe Gly Arg Leu Leu  
                   165                  170                  175  
 Glu Arg Gly Val Ala Tyr Gly Ala Met Phe Pro Gly Asp Glu Asn Thr  
           180                  185                  190  
 Met His Gln Ala Asn Glu Tyr Met Pro Leu Glu Asn Ile Phe Arg Ser  
           195                  200                  205  
 Ala Ala Ile Tyr Ala Glu Ala Ile Tyr Glu Leu Ile Lys  
           210                  215                  220

<210> 24  
 <211> 194  
 <212> PRT  
 <213> streptococcus

<400> 24

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Met Thr Asp Leu Glu Lys Ile Ile Lys Ala Ile Lys Ser Asp Ser Gln
 1          5          10          15
Asn Gln Asn Tyr Thr Glu Asn Gly Ile Asp Pro Leu Phe Ala Ala Pro
          20          25          30
Lys Thr Ala Arg Ile Asn Ile Val Gly Gln Ala Pro Gly Leu Lys Thr
          35          40          45
Gln Glu Ala Arg Leu Tyr Trp Lys Asp Lys Ser Gly Asp Arg Leu Arg
 50          55          60
Gln Trp Leu Gly Val Asp Glu Glu Thr Phe Tyr His Ser Gly Lys Phe
65          70          75          80
Ala Val Leu Pro Leu Asp Phe Tyr Tyr Pro Gly Lys Gly Lys Ser Gly
          85          90          95
Asp Leu Pro Pro Arg Lys Gly Phe Ala Glu Lys Trp His Pro Leu Ile
          100          105          110
Leu Lys Glu Met Pro Asn Val Gln Leu Thr Leu Leu Val Gly Gln Tyr
          115          120          125
Ala Gln Lys Tyr Tyr Leu Gly Ser Ser Ala His Lys Asn Leu Thr Glu
          130          135          140
Thr Val Lys Ala Tyr Lys Asp Tyr Leu Pro Asp Tyr Leu Pro Leu Val
145          150          155          160
His Pro Ser Pro Arg Asn Gln Ile Trp Leu Lys Lys Asn Pro Trp Phe
          165          170          175
Glu Lys Asp Leu Ile Val Asp Leu Gln Lys Ile Val Ala Asp Ile Leu
          180          185          190
Lys Asp

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<210> 25
<211> 126
<212> PRT
<213> streptococcus

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<400> 25
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Ala Phe Glu Asp Tyr Ile Asn Gly Phe Thr Gly Glu Phe Ile Thr Thr
          20          25          30
Glu His Phe Asp Leu Ser Asn Pro Tyr Thr Gly Gln Asp Asp Val Pro
          35          40          45
Asp Tyr Ser Ala Tyr Cys Gln Lys Ile Asp Tyr Leu Asn Gln Lys Tyr
 50          55          60
Gly Asn Arg Phe Lys Lys Gly Ile Glu Ile Gly Tyr Phe Lys Asp Arg
65          70          75          80
Glu Ser Asp Ile Leu Asp Tyr Leu Lys Asn Lys Glu Phe Asp Leu Lys
          85          90          95
Leu Leu Ser Ile His His Asn Gly Arg Tyr Asp Tyr Leu Gln Glu Glu
          100          105          110
Ala Leu Lys Val Pro Thr Lys Gly Ala Phe Ser Arg Leu Leu
          115          120          125

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<210> 26
<211> 931
<212> PRT
<213> streptococcus

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<400> 26

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Met	Lys	Arg	Lys	Asp	Leu	Phe	Gly	Asp	Lys	Gln	Thr	Gln	Tyr	Thr	Ile
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Arg	Lys	Leu	Ser	Val	Gly	Val	Ala	Ser	Val	Thr	Thr	Gly	Val	Cys	Ile
			20					25					30		
Phe	Leu	His	Ser	Pro	Gln	Val	Phe	Ala	Glu	Glu	Val	Ser	Val	Ser	Pro
		35					40					45			
Ala	Thr	Thr	Ala	Ile	Ala	Glu	Ser	Asn	Ile	Asn	Gln	Val	Asp	Asn	Gln
	50					55				60					
Gln	Ser	Thr	Asn	Leu	Lys	Asp	Asp	Ile	Asn	Ser	Asn	Ser	Glu	Thr	Val
65				70					75					80	
Val	Thr	Pro	Ser	Asp	Met	Pro	Asp	Thr	Lys	Gln	Leu	Val	Ser	Asp	Glu
			85					90						95	
Thr	Asp	Thr	Gln	Lys	Gly	Val	Thr	Glu	Pro	Asp	Lys	Ala	Thr	Ser	Leu
			100					105					110		
Leu	Glu	Glu	Asn	Lys	Gly	Pro	Val	Ser	Asp	Lys	Asn	Thr	Leu	Asp	Leu
		115				120						125			
Lys	Val	Ala	Pro	Ser	Thr	Leu	Gln	Asn	Thr	Pro	Asp	Lys	Thr	Ser	Gln
	130					135					140				
Ala	Ile	Gly	Ala	Pro	Ser	Pro	Thr	Leu	Lys	Val	Ala	Asn	Gln	Ala	Pro
145				150						155				160	
Arg	Ile	Glu	Asn	Gly	Tyr	Phe	Arg	Leu	His	Leu	Lys	Glu	Leu	Pro	Gln
			165					170						175	
Gly	His	Pro	Val	Glu	Ser	Thr	Gly	Leu	Trp	Ile	Trp	Gly	Asp	Val	Asp
			180					185					190		
Gln	Pro	Ser	Ser	Asn	Trp	Pro	Asn	Gly	Ala	Ile	Pro	Met	Thr	Asp	Ala
		195				200						205			
Lys	Lys	Asp	Asp	Tyr	Gly	Tyr	Tyr	Val	Asp	Phe	Lys	Leu	Ser	Glu	Lys
	210				215						220				
Gln	Arg	Lys	Gln	Ile	Ser	Phe	Leu	Ile	Asn	Asn	Lys	Ala	Gly	Thr	Asn
225				230						235				240	
Leu	Ser	Gly	Asp	His	His	Ile	Pro	Leu	Leu	Arg	Pro	Glu	Met	Asn	Gln
			245					250						255	
Val	Trp	Ile	Asp	Glu	Lys	Tyr	Gly	Ile	His	Thr	Tyr	Gln	Pro	Leu	Lys
		260					265						270		
Glu	Gly	Tyr	Val	Arg	Ile	Asn	Tyr	Leu	Ser	Ser	Ser	Ser	Asn	Tyr	Asp
	275					280						285			
His	Leu	Ser	Ala	Trp	Leu	Phe	Lys	Asp	Val	Ala	Thr	Xaa	Ser	Thr	Thr
	290				295						300				
Trp	Pro	Asp	Gly	Ser	Asn	Phe	Val	Asn	Gln	Gly	Leu	Tyr	Gly	Arg	Tyr
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Ile	Asp	Val	Ser	Leu	Lys	Thr	Asn	Ala	Lys	Glu	Ile	Gly	Phe	Leu	Ile
			325					330						335	
Leu	Asp	Glu	Ser	Lys	Thr	Gly	Asp	Ala	Val	Lys	Val	Gln	Pro	Asn	Asp
		340						345					350		
Tyr	Val	Phe	Arg	Asp	Leu	Ala	Asn	His	Asn	Gln	Ile	Phe	Val	Lys	Asp
	355				360							365			
Lys	Asp	Pro	Lys	Val	Tyr	Asn	Asn	Pro	Tyr	Tyr	Ile	Asp	Gln	Val	Gln
	370				375						380				
Leu	Lys	Asp	Ala	Gln	Gln	Ile	Asp	Leu	Thr	Ser	Ile	Gln	Ala	Ser	Phe
385				390						395				400	
Thr	Thr	Leu	Asp	Gly	Val	Asp	Lys	Thr	Glu	Ile	Leu	Lys	Glu	Leu	Lys
			405					410						415	
Val	Thr	Asp	Lys	Asn	Gln	Asn	Ala	Ile	Gln	Ile	Ser	Asp	Ile	Thr	Leu
		420					425						430		
Asp	Thr	Ser	Lys	Ser	Leu	Leu	Ile	Ile	Lys	Gly	Asp	Phe	Asn	Pro	Lys
	435					440						445			

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Gln	Gly	His	Phe	Asn	Ile	Ser	Tyr	Asn	Gly	Asn	Asn	Val	Met	Thr	Arg
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Gln	Ser	Trp	Glu	Phe	Lys	Asp	Gln	Leu	Tyr	Ala	Tyr	Ser	Gly	Asn	Leu
465					470					475					480
Gly	Ala	Val	Leu	Asn	Gln	Asp	Gly	Ser	Lys	Val	Glu	Ala	Ser	Leu	Trp
				485					490					495	
Ser	Pro	Ser	Ala	Asp	Ser	Val	Thr	Met	Ile	Ile	Tyr	Asp	Lys	Asp	Asn
			500					505					510		
Gln	Asn	Arg	Val	Val	Ala	Thr	Thr	Pro	Leu	Val	Lys	Asn	Asn	Lys	Gly
		515					520					525			
Val	Trp	Gln	Thr	Ile	Leu	Asp	Thr	Lys	Leu	Gly	Ile	Lys	Asn	Tyr	Thr
	530					535					540				
Gly	Tyr	Tyr	Tyr	Leu	Tyr	Glu	Ile	Lys	Arg	Gly	Lys	Asp	Lys	Val	Lys
545					550					555					560
Ile	Leu	Asp	Pro	Tyr	Ala	Lys	Ser	Leu	Ala	Glu	Trp	Asp	Ser	Asn	Thr
				565					570					575	
Val	Asn	Asp	Asp	Ile	Lys	Thr	Ala	Lys	Ala	Ala	Phe	Val	Asn	Pro	Ser
			580					585					590		
Gln	Leu	Gly	Pro	Gln	Asn	Leu	Ser	Phe	Ala	Lys	Ile	Ala	Asn	Phe	Lys
		595					600					605			
Gly	Arg	Gln	Asp	Ala	Val	Ile	Tyr	Glu	Ala	His	Val	Arg	Asp	Phe	Thr
	610					615					620				
Ser	Asp	Arg	Ser	Leu	Asp	Gly	Lys	Leu	Lys	Asn	Gln	Phe	Gly	Thr	Phe
625					630					635					640
Ala	Ala	Phe	Ser	Glu	Lys	Leu	Asp	Tyr	Leu	Gln	Lys	Leu	Gly	Val	Thr
				645					650					655	
His	Ile	Gln	Leu	Leu	Pro	Val	Leu	Ser	Tyr	Phe	Tyr	Val	Asn	Glu	Met
			660					665					670		
Asp	Lys	Ser	Arg	Ser	Thr	Ala	Tyr	Thr	Ser	Ser	Asp	Asn	Asn	Tyr	Asn
		675					680					685			
Trp	Gly	Tyr	Asp	Pro	Gln	Ser	Tyr	Phe	Ala	Leu	Ser	Gly	Met	Tyr	Ser
	690					695					700				
Glu	Lys	Pro	Lys	Asp	Pro	Ser	Ala	Arg	Ile	Ala	Glu	Leu	Lys	Gln	Leu
705					710					715					720
Ile	His	Asp	Ile	His	Lys	Arg	Gly	Met	Gly	Val	Ile	Leu	Asp	Val	Val
				725					730					735	
Tyr	Asn	His	Thr	Ala	Lys	Thr	Tyr	Leu	Phe	Glu	Asp	Ile	Glu	Pro	Asn
			740				745						750		
Tyr	Tyr	His	Phe	Met	Asn	Glu	Asp	Gly	Ser	Pro	Arg	Glu	Ser	Phe	Gly
		755					760					765			
Gly	Gly	Arg	Leu	Gly	Thr	Thr	His	Ala	Met	Ser	Arg	Arg	Val	Leu	Val
	770					775					780				
Asp	Ser	Ile	Lys	Tyr	Leu	Thr	Ser	Glu	Phe	Lys	Val	Asp	Gly	Phe	Arg
785					790					795					800
Phe	Asp	Met	Met	Gly	Asp	His	Asp	Ala	Ala	Ala	Ile	Glu	Leu	Ala	Tyr
				805					810					815	
Lys	Glu	Ala	Lys	Ala	Ile	Asn	Pro	Asn	Met	Ile	Met	Ile	Gly	Glu	Gly
			820					825					830		
Trp	Arg	Thr	Phe	Gln	Gly	Asp	Gln	Gly	Gln	Pro	Val	Lys	Pro	Ala	Asp
		835					840					845			
Gln	Asp	Trp	Met	Lys	Ser	Thr	Asp	Thr	Val	Gly	Val	Phe	Ser	Asp	Asp
	850					855					860				
Ile	Arg	Asn	Ser	Leu	Lys	Ser	Gly	Phe	Pro	Asn	Glu	Gly	Thr	Pro	Ala
865					870					875					880
Phe	Ile	Thr	Gly	Gly	Pro	Gln	Ser	Leu	Gln	Gly	Ile	Phe	Lys	Asn	Ile
				885					890					895	

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Lys Ala Gln Pro Gly Asn Phe Glu Ala Asp Ser Pro Gly Asp Val Val  
                   900                  905                  910  
 Gln Tyr Ile Ala Ala His Asp Asn Leu Thr Leu His Asp Val Ile Ala  
                   915                  920                  925  
 Lys Ser Ile  
                   930

&lt;210&gt; 27

&lt;211&gt; 5607

&lt;212&gt; DNA

&lt;213&gt; streptococcus

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (2)...(301)

&lt;400&gt; 27

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 Ile Gln Ser Leu Thr Glu Gly Gln Leu Arg Ser Asp Ile Pro Glu Phe  
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cgt gct ggt gat act gta cgt gtt cac gct aaa gtt gtt gaa ggt act 97  
 Arg Ala Gly Asp Thr Val Arg Val His Ala Lys Val Val Glu Gly Thr  
                   20                  25                  30

cgc gaa cgt att cag atc ttt gaa ggt gtt gtt atc tca cgt aaa ggt 145  
 Arg Glu Arg Ile Gln Ile Phe Glu Gly Val Val Ile Ser Arg Lys Gly  
                   35                  40                  45

caa gga atc tca gaa atg tac aca gta cgt aaa att tct ggt ggt atc 193  
 Gln Gly Ile Ser Glu Met Tyr Thr Val Arg Lys Ile Ser Gly Gly Ile  
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ggt gta gag cgt aca ttc cca att cac act cct cgt gtt gat aaa atc 241  
 Gly Val Glu Arg Thr Phe Pro Ile His Thr Pro Arg Val Asp Lys Ile  
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gaa gtt gtt cgt tat ggt aaa gta cgt cgt gct aaa ctt tac tac tta 289  
 Glu Val Val Arg Tyr Gly Lys Val Arg Arg Ala Lys Leu Tyr Tyr Leu  
                   85                  90                  95

cgc gca ttg caa ggtaaagctg cacgtattaa agaaatccgt cgtaaatttt 341  
 Arg Ala Leu Gln  
                   100

gatgatcaga ttttaaaaaat gcttggttgt ttgaggatag taactatggt ttaaaactgg 401  
 acaaccaaga cgtaaaaaat ctgcctgtgg gcagtttttt tactaggtcc ccttagttca 461  
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&lt;210&gt; 28

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; streptococcus

&lt;400&gt; 28

```

Ile Gln Ser Leu Thr Glu Gly Gln Leu Arg Ser Asp Ile Pro Glu Phe
 1           5           10           15
Arg Ala Gly Asp Thr Val Arg Val His Ala Lys Val Val Glu Gly Thr
          20           25           30
Arg Glu Arg Ile Gln Ile Phe Glu Gly Val Val Ile Ser Arg Lys Gly
          35           40           45
Gln Gly Ile Ser Glu Met Tyr Thr Val Arg Lys Ile Ser Gly Gly Ile
          50           55           60
Gly Val Glu Arg Thr Phe Pro Ile His Thr Pro Arg Val Asp Lys Ile
65           70           75           80
Glu Val Val Arg Tyr Gly Lys Val Arg Arg Ala Lys Leu Tyr Tyr Leu
          85           90           95
Arg Ala Leu Gln Gly Lys Ala Ala Arg Ile Lys Glu Ile Arg Arg
          100          105          110

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&lt;210&gt; 29

&lt;211&gt; 173

&lt;212&gt; PRT

&lt;213&gt; streptococcus

&lt;400&gt; 29

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Met Arg Phe Ala Glu Cys Leu Gly Leu Thr Val Asn Asp Ile Asp Tyr
 1           5           10           15
Thr Asn Lys Tyr Leu Ser Ile Asn Lys Thr Trp Asp Tyr His Phe Asn
          20           25           30
Gln Arg Tyr Leu Pro Thr Lys Asn Lys Ser Ser Ile Arg Asn Ile Pro
          35           40           45
Ile Asp Asn Asp Thr Leu Phe Phe Leu His Glu Phe Thr Lys Asn Lys

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50	55	60
Asn Asp Arg Leu Phe	Asp Lys Leu Ser Asn	Asn Ala Val Asn Lys Thr
65	70	75
Ile Arg Lys Ile Thr	Gly Arg Glu Val Arg	Val His Ser Leu Arg His
	85	90
Thr Phe Ala Ser Tyr	Leu Ile Ser Ile Ser	Gln Val Leu Asp His Glu
	100	105
Asn Leu Asn Ile Thr	Leu Glu Val Tyr Ala	His Gln Leu Gln Glu Gln
	115	120
Lys Asp Arg Asn Asp	Lys Leu Asn Gln Arg	Asn Leu Gly Gln Asn Ser
	130	135
Ser Lys Pro Leu Phe	Thr Cys Asn Glu Tyr	Val Pro Cys Arg Asn Arg
145	150	155
Thr Ser Asn Tyr Ser	Leu Gly Gly Ser Cys	Tyr Ile His
	165	170

<210> 30  
 <211> 389  
 <212> PRT  
 <213> streptococcus

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35 40 45
Gln Tyr Asp Gly Leu Ala Lys Leu Lys Asp Leu Lys Val Val Ser Gly
50 55 60
Glu Gln Ser Ile Asn Arg Glu Asp Leu Ser Asp Glu Phe Lys Asn Val
65 70 75 80
Val Ser Leu Glu Ala Thr Ser Asn Thr Lys Arg Asn Leu Leu Phe Ser
85 90 95
Ser Gly Val Phe Ser Phe Lys Glu Gly Lys Asn Ile Glu Glu Asn Asp
100 105 110
Lys Asn Ser Ile Leu Val His Glu Glu Phe Ala Lys Gln Asn Lys Leu
115 120 125
Lys Leu Gly Asp Glu Ile Asp Leu Glu Leu Leu Asp Thr Glu Lys Ser
130 135 140
Gly Lys Ile Lys Ser His Lys Phe Lys Ile Ile Gly Ile Phe Ser Gly
145 150 155 160
Lys Lys Gln Glu Thr Tyr Thr Gly Leu Ser Ser Asp Phe Ser Glu Asn
165 170 175
Met Val Phe Val Asp Tyr Ser Thr Ser Gln Glu Ile Leu Asn Lys Ser
180 185 190
Glu Asn Asn Arg Ile Ala Asn Lys Ile Leu Met Tyr Ser Gly Ser Leu
195 200 205
Glu Ser Thr Glu Leu Ala Leu Asn Lys Leu Lys Asp Phe Lys Ile Asp
210 215 220
Lys Ser Lys Tyr Ser Ile Lys Lys Asp Asn Lys Ala Phe Glu Glu Ser
225 230 235 240
Leu Glu Ser Val Ser Gly Ile Lys His Ile Ile Lys Ile Met Thr Tyr
245 250 255
Ser Ile Met Leu Gly Gly Ile Val Val Leu Ser Leu Ile Leu Ile Leu
260 265 270

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Trp Leu Arg Glu Arg Ile Tyr Glu Ile Gly Ile Phe Leu Ser Ile Gly  
 275 280 285  
 Thr Thr Lys Ile Gln Ile Ile Arg Gln Phe Ile Phe Glu Leu Ile Phe  
 290 295 300  
 Ile Ser Ile Pro Ser Ile Ile Ser Ser Leu Phe Leu Gly Asn Leu Leu  
 305 310 315 320  
 Leu Lys Val Ile Val Glu Gly Phe Ile Asn Ser Glu Asn Ser Met Ile  
 325 330 335  
 Phe Gly Gly Ser Leu Ile Asn Lys Ser Ser Phe Met Leu Asn Ile Thr  
 340 345 350  
 Thr Leu Ala Glu Ser Tyr Leu Ile Leu Ile Ser Ile Ile Val Leu Ser  
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 Leu Ser Lys Ile Ser  
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<210> 31  
 <211> 169  
 <212> PRT  
 <213> streptococcus

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 Lys Glu Lys Val Leu Ser Gly Val Asn Gln Lys Phe Glu Leu Gly Lys  
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 Phe Tyr Ala Ile Val Gly Lys Ser Gly Thr Gly Lys Ser Thr Leu Leu  
 35 40 45  
 Ser Leu Leu Ala Gly Leu Asp Lys Val Gln Thr Gly Lys Ile Leu Phe  
 50 55 60  
 Lys Asn Glu Asp Ile Glu Lys Lys Gly Tyr Ser Asn His Arg Lys Asn  
 65 70 75 80  
 Asn Ile Ser Leu Val Phe Gln Asn Tyr Asn Leu Ile Asp Tyr Leu Ser  
 85 90 95  
 Pro Ile Glu Asn Ile Arg Leu Val Asn Lys Ser Val Asp Glu Ser Ile  
 100 105 110  
 Leu Phe Glu Leu Gly Leu Asp Lys Lys Gln Ile Lys Arg Asn Val Met  
 115 120 125  
 Lys Leu Ser Gly Gly Gln Gln Gln Arg Val Ala Ile Ala Arg Ala Leu  
 130 135 140  
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 145 150 155 160  
 Asp Ser Val Thr Ala Gly Glu Ile Ile  
 165

<210> 32  
 <211> 4171  
 <212> DNA  
 <213> Streptococcus

<400> 32  
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 ttttcaatgg gaagtctctg gccactttca atactaacca attgattcgc gaagttgtct 180  
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ttatcagacc	cactaccgag	catactatcc	ccacgatgat	gacagctagc	ccctatcatc	300
aaggtatcaa	tgatcctgcc	gcagaccaaa	aaacatacca	aatggagggt	gcgctagcag	360
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<210> 33
<211> 649
<212> PRT
<213> Streptococcus

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<400> 33
Tyr Asp Asn Ile Phe Gln Ser Leu His His Leu Leu Ala Cys Arg Gly
 1          5          10          15
Lys Ser Gly Asn Thr Leu Ile Asp Gln Leu Val Ala Asp Gly Leu Leu
 20          25          30
His Ala Asp Asn His Tyr His Phe Asn Gly Lys Ser Leu Ala Thr
 35          40          45
Phe Asn Thr Asn Gln Leu Ile Arg Glu Val Val Tyr Val Glu Ile Ser
 50          55          60
Leu Asp Thr Met Ser Ser Gly Glu His Asp Leu Val Lys Val Asn Ile
 65          70          75          80
Ile Arg Pro Thr Thr Glu His Thr Ile Pro Thr Met Met Thr Ala Ser
 85          90          95
Pro Tyr His Gln Gly Ile Asn Asp Pro Ala Ala Asp Gln Lys Thr Tyr
100          105          110
Gln Met Glu Gly Ala Leu Ala Val Lys Gln Pro Lys His Ile Gln Val
115          120          125
Asp Thr Lys Pro Phe Lys Glu Glu Val Lys His Pro Ser Lys Leu Pro
130          135          140
Ile Ser Pro Ala Thr Glu Ser Phe Thr His Ile Asp Ser Tyr Ser Leu
145          150          155          160
Asn Asp Tyr Phe Leu Ser Arg Gly Phe Ala Asn Ile Tyr Val Ser Gly
165          170          175
Val Gly Thr Ala Gly Ser Thr Gly Phe Met Thr Ser Gly Asp Tyr Gln
180          185          190
Gln Ile Gln Ser Phe Lys Ala Val Ile Asp Trp Leu Asn Gly Lys Val
195          200          205
Thr Ala Phe Thr Ser His Lys Arg Asp Lys Gln Val Lys Ala Asp Trp
210          215          220
Ser Asn Gly Leu Val Ala Thr Thr Gly Lys Ser Tyr Leu Gly Thr Met
225          230          235          240
Ser Thr Gly Leu Ala Thr Thr Gly Val Glu Gly Leu Lys Val Ile Ile
245          250          255
Ala Glu Ala Ala Ile Ser Thr Trp Tyr Asp Tyr Tyr Arg Glu Asn Gly
260          265          270
Leu Val Cys Ser Pro Gly Gly Tyr Pro Gly Glu Asp Leu Asp Val Leu
275          280          285
Thr Glu Leu Thr Tyr Ser Arg Asn Leu Leu Ala Gly Asp Tyr Ile Lys
290          295          300
Asn Asn Asp Cys Tyr Gln Ala Leu Leu Asn Glu Gln Ser Lys Ala Ile

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305          310          315          320
Asp Arg Gln Ser Gly Asp Tyr Asn Gln Tyr Trp His Asp Arg Asn Tyr
325          330          335
Leu Thr His Val Asn Asn Val Lys Ser Arg Val Val Tyr Thr His Gly
340          345          350
Leu Gln Asp Trp Asn Val Lys Pro Arg His Val Tyr Lys Val Phe Asn
355          360          365
Ala Leu Pro Gln Thr Ile Lys Lys His Leu Phe Leu His Gln Gly Gln
370          375          380
His Val Tyr Met His Asn Trp Gln Ser Ile Asp Phe Arg Glu Ser Met
385          390          395          400
Asn Ala Leu Leu Ser Gln Glu Leu Leu Gly Ile Asp Asn His Phe Gln
405          410          415
Leu Glu Glu Val Ile Trp Gln Asp Asn Thr Thr Glu Gln Thr Trp Gln
420          425          430
Val Leu Asp Ala Phe Gly Gly Asn His Gln Glu Gln Ile Gly Leu Gly
435          440          445
Asp Ser Lys Lys Leu Ile Asp Asn His Tyr Asp Lys Glu Ala Phe Asp
450          455          460
Thr Tyr Cys Lys Asp Phe Asn Val Phe Lys Asn Asp Leu Phe Lys Gly
465          470          475          480
Asn Asn Lys Thr Asn Gln Ile Thr Ile Asn Leu Pro Leu Lys Lys Asn
485          490          495
Tyr Leu Leu Asn Gly Gln Cys Lys Leu His Leu Arg Val Lys Thr Ser
500          505          510
Asp Lys Lys Ala Ile Leu Ser Ala Gln Ile Leu Asp Tyr Gly Pro Lys
515          520          525
Lys Arg Phe Lys Asp Thr Pro Thr Ile Lys Phe Leu Asn Ser Leu Asp
530          535          540
Asn Gly Lys Asn Phe Ala Arg Glu Ala Leu Arg Glu Leu Pro Phe Thr
545          550          555          560
Lys Asp His Tyr Arg Val Ile Ser Lys Gly Val Leu Asn Leu Gln Asn
565          570          575
Arg Thr Asp Leu Leu Thr Ile Glu Ala Ile Glu Pro Glu Gln Trp Phe
580          585          590
Asp Ile Glu Phe Ser Leu Gln Pro Ser Ile Tyr Gln Leu Ser Lys Gly
595          600          605
Asp Asn Leu Arg Ile Ile Leu Tyr Thr Thr Asp Phe Glu His Thr Ile
610          615          620
Arg Asp Asn Ala Ser Tyr Ser Ile Thr Val Asp Leu Ser Gln Ser Tyr
625          630          635          640
Leu Thr Ile Pro Thr Asn Gln Gly Asn
645

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<210> 34
<211> 119
<212> PRT
<213> Streptococcus

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Met Lys Leu Leu Thr Lys Glu Arg Phe Asp Asp Ser Gln His Phe Trp
1          5          10          15
Tyr Gln Ile Asn Leu Leu Gln Glu Ser Asn Phe Gly Ala Val Phe Asp
20          25          30
His Asp Asn Lys Asn Ile Pro Gln Val Val Ala Thr Ile Val Asp Asp
35          40          45

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Leu Gln Gly Ser Gly Ser Ser Asn His Phe Trp Tyr Phe Gly Asn Thr  
 50 55 60  
 Thr Asp Thr Ser Ile Leu Met Ile Ala His Leu Asn Arg Lys Phe Tyr  
 65 70 75 80  
 Ile Gln Val Asn Leu Lys Asp Phe Asp Phe Ala Leu Asn Leu Ile Ala  
 85 90 95  
 Ile Asn Asn Trp Lys Ser Leu Leu Gln Thr Gln Leu Glu Ala Leu Asn  
 100 105 110  
 Asp Thr Leu Ala Ile Phe Gln  
 115

<210> 35  
 <211> 326  
 <212> PRT  
 <213> Streptococcus

<400> 35  
 Met Ser Ser Tyr Trp Asn Asn Tyr Pro Glu Leu Lys Lys Asn Ile Asp  
 1 5 10 15  
 Glu Thr Asn Gln Leu Ile Gln Glu Arg Ile Gln Val Arg Asn Lys Asp  
 20 25 30  
 Ile Glu Ala Ala Leu Ser Gln Leu Thr Ala Ala Gly Gly Lys Gln Leu  
 35 40 45  
 Arg Pro Ala Phe Phe Tyr Leu Phe Ser Gln Leu Gly Asn Lys Glu Asn  
 50 55 60  
 Gln Asp Thr Gln Gln Leu Lys Lys Ile Ala Ala Ser Leu Glu Ile Leu  
 65 70 75 80  
 His Val Ala Thr Leu Ile His Asp Asp Val Ile Asp Asp Ser Pro Leu  
 85 90 95  
 Arg Arg Gly Asn Met Thr Ile Gln Ser Lys Phe Gly Lys Asp Ile Ala  
 100 105 110  
 Val Tyr Thr Gly Asp Leu Leu Phe Thr Val Phe Phe Asp Leu Ile Leu  
 115 120 125  
 Glu Ser Met Thr Asp Thr Pro Phe Met Arg Ile Asn Ala Lys Ser Met  
 130 135 140  
 Arg Lys Ile Leu Met Gly Glu Leu Asp Gln Met His Leu Arg Tyr Asn  
 145 150 155 160  
 Gln Gln Gln Gly Ile His His Tyr Leu Arg Ala Ile Ser Gly Lys Thr  
 165 170 175  
 Ala Glu Leu Phe Lys Leu Ala Ser Lys Glu Gly Ala Tyr Phe Gly Gly  
 180 185 190  
 Ala Glu Lys Glu Val Val Arg Leu Ala Gly His Ile Gly Phe Asn Ile  
 195 200 205  
 Gly Met Thr Phe Gln Ile Leu Asp Asp Ile Leu Asp Tyr Thr Ala Asp  
 210 215 220  
 Lys Lys Thr Phe Asn Lys Pro Val Leu Glu Asp Leu Thr Gln Gly Val  
 225 230 235 240  
 Tyr Ser Leu Pro Leu Leu Leu Ala Ile Glu Glu Asn Pro Asp Ile Phe  
 245 250 255  
 Lys Pro Ile Leu Asp Lys Lys Thr Asp Met Ala Thr Glu Asp Met Glu  
 260 265 270  
 Lys Ile Ala Tyr Leu Val Val Ser His Arg Gly Val Asp Lys Ala Arg  
 275 280 285  
 His Leu Ala Arg Lys Phe Thr Glu Lys Ala Ile Ser Asp Ile Asn Lys  
 290 295 300  
 Leu Pro Gln Asn Ser Ala Lys Lys Gln Leu Leu Gln Leu Thr Asn Tyr

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305                                  310  
Leu Leu Lys Arg Lys Ile  
                                325

315

320

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<210> 36
<211> 247
<212> PRT
<213> Streptococcus
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Lys 65	Ile	Thr	Leu	Gly 70	Gly	Ala	Asp	Val	Ser	Ile 75	Val	Gly	Asp 80	Cys	Ile
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Thr	Leu	Leu	Asn 100	Asn	Ile	Arg	Ile	Gly 105	Asn	Gln	Asp	Ala	Ser 110	Glu	Glu
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&lt;211&gt; 306

&lt;212&gt; PRT

&lt;213&gt; Streptococcus

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 Val Met Ile Gln His Ala Asp Gly Met His Ser Gly Tyr Ala His Met  
 100 105 110  
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 130 135 140  
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&lt;211&gt; 232

&lt;212&gt; PRT

&lt;213&gt; Streptococcus

&lt;400&gt; 40

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&lt;210&gt; 43

&lt;211&gt; 1230

&lt;212&gt; DNA

&lt;213&gt; Streptococcus

&lt;400&gt; 43

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&lt;210&gt; 44

&lt;211&gt; 409

&lt;212&gt; PRT

&lt;213&gt; Streptococcus

&lt;400&gt; 44

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20           25           30
Gly Asp Thr Leu Ser Val Ile Ser Glu Ala Met Ser Ile Asp Met Asn

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12N 15/31, C07K 14/315, A61K 39/09,</b> <b>C12N 1/21</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 99/42588</b>  <b>(43) International Publication Date:</b> 26 August 1999 (26.08.99)
<b>(21) International Application Number:</b> PCT/CA99/00114  <b>(22) International Filing Date:</b> 17 February 1999 (17.02.99)  <b>(30) Priority Data:</b> 60/075,425                      20 February 1998 (20.02.98)                      US  <b>(71) Applicant (for all designated States except US):</b> BIOCHEM VACCINS INC. [CA/CA]; 2323 boulevard du Parc Technologique, Sainte-Foy, Québec G1P 4R8 (CA).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BRODEUR, Bernard, R. [CA/CA]; 2401 rue Maritain, Sillery, Québec G1T 1N6 (CA). RIOUX, Clément [CA/CA]; 1012 Jean-Charles Cantin, Ville de Cap Rouge, Québec G1Y 2X1 (CA). BOYER, Martine [CA/CA]; Apt. 204, 25 des Mouettes, Beauport, Québec G1E 7G1 (CA). CHARLEBOIS, Isabelle [CA/CA]; 410 Mirabel, St-Nicolas, Québec G7A 2L5 (CA). HAMEL, Josée [CA/CA]; 2401 rue Maritain, Sillery, Québec G1T 1N6 (CA). MARTIN, Denis [CA/CA]; 4728-G rue Gaboury, St-Augustin-de-Desmaures, Québec G3A 1E9 (CA).		<b>(74) Agents:</b> CÔTE, France et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montréal, Québec H3A 2Y3 (CA).  <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>  <b>(88) Date of publication of the international search report:</b> 23 March 2000 (23.03.00)
<b>(54) Title:</b> GROUP B STREPTOCOCCUS ANTIGENS		
<b>(57) Abstract</b>  Group B streptococcus (GBS) proteins and polynucleotides encoding them are disclosed. Said proteins are antigenic and therefore useful vaccine components for the prophylaxis or therapy of streptococcus infection in animals. Also disclosed are recombinant methods of producing the protein antigens as well as diagnostic assays for detecting streptococcus bacterial infection.		

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CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00114

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/31 C07K14/315 A61K39/09 C12N1/21

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MICHEL J L ET AL: "Cloned alpha and beta C-protein antigens of group B Streptococci elicit protective immunity" INFECTION AND IMMUNITY., vol. 59, no. 6, June 1991 (1991-06), pages 2023-2028, XP002107260 AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON., US ISSN: 0019-9567 the whole document --- -/--	1-48



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

15 December 1999

Date of mailing of the international search report

24 01 2000

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00114

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LACHENAUER C S ET AL: "Cloning and expression in Escherichia coli of a protective surface protein from type V group B Streptococci" ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, vol. 418, 9 December 1997 (1997-12-09), pages 615-618, XP002107261 SPRING ST., NY, US ISSN: 0065-2598 the whole document	1-48
P,X	--- DATABASE EMBL [Online] Accession number AF062533, 11 February 1999 (1999-02-11) SPELLERBERG B ET AL: "Streptococcus agalactiae Lmb (lmb) gene, complete cds; and unknown gene." XP002125180 98.9% identity between base 1-2514 of SEQ ID NO 13 and base 988-3501 of AF062533 Translation product (AC: Q9ZHG9) has 98.5% identity in 793 AA overlap with SEQ ID NO 15 and 98.5% identity in 715 AA overlap with SEQ ID 16 & SPELLERBERG B ET AL: "Lmb, a protein with similarities to the Lral adhesin family, mediates attachment of Streptococcus agalactiae to human laminin" INFECTION AND IMMUNITY., vol. 67, no. 2, February 1999 (1999-02), pages 871-878, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON., US ISSN: 0019-9567	1-10, 16-23,26
X	--- DATABASE EMBL [Online] Accession Number L23843, 4 January 1994 (1994-01-04) MACRINA F L ET AL: "ISN IS199 from Streptococcus mutans IS3 (Brathall serotype C) DNA fragment" XP002125181 79.6% identity between base 5212-4314 of SEQ ID NO 13 and base 312-1220 of L23843 Translation has 83.4% identity in 283 AA overlap with SEQ ID NO 21 --- -/--	1,3-7,10

# INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/CA 99/00114

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL [Online]  Accession Number AF026542,  15 October 1997 (1997-10-15)  HYNES W L ET AL: "Streptococcus pyogenes  FF22 lantibiotic (scn) gene cluster region  containing: scnK, scnR, streptococin  A-FF22 precursor (scnA), scnA1, scnM,  scnT, scnF, scnE, scnG genes, complete  cds, and tnpA gene, partial cds."  XP002125182  88.2% identity between base 2607-2953 of  SEQ ID NO 13 and base 10435-10777 of  AF026542  Translation product (AC: 031057) has 95.8%  identity in 71 AA overlap with SEQ ID NO  17</p> <p style="text-align: center;">---</p>	<p>1-10,  16-23,26</p>
P,X	<p>DATABASE GENESEQ [Online]  Accession Number V52136,  23 October 1998 (1998-10-23)  BARASH S C ET AL: "Streptococcus  pneumoniae genome fragment SEQ ID NO:3"  XP002125183  68.5% identity between base 2539-3319 of  SEQ ID NO 37 and base 18492-19271 of  V52136  Translation has 74.5% identity in 231 AA  overlap with SEQ ID NO 40  &amp; WO 98 18931 A (DOUGHERTY BRIAN A ;HUMAN  GENOME SCIENCES INC (US); ROSEN CRAIG A)  7 May 1998 (1998-05-07)</p> <p style="text-align: center;">-----</p>	<p>1,3-7,10</p>

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 99/00114

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 37-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,  
no additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
  
11-14, 16, 24, 25, 27, 28, 30, 31 (completely), 1-10, 15, 17-23, 26, 29, 32-48 (all partially) i.e. (group of) inventions 1, 3 and 7
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10,15,17-23,26,29,32-48 (all partially)

An isolated polynucleotide encoding a polypeptide having a sequence selected from the group consisting of SEQ ID 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6 i.e. the open reading frames of clone 1 (SEQ ID NO 1). Also a vector comprising the polynucleotide, a host cell transformed therewith, an isolated polypeptide encoded by the polynucleotide, a vaccine composition comprising said polypeptide and a polynucleotide having a sequence SEQ ID NO 1.

2. Claims: 1-10,15,17-23,26,29,32-48 (all partially)

Same as invention 1, but directed at polypeptides of clone 2 (SEQ ID 7) with sequences SEQ ID NO 8-12.

3. Claims: 1-10,15,17-23,26,29,32-48 (all partially)

Same as invention 1, but directed at polypeptides of clone 3 (SEQ ID 13) with sequences SEQ ID NO 14-21.

4. Claims: 1-10,15,17-23,26,29,32-48 (all partially)

Same as invention 1, but directed at polypeptides of clone 4 (SEQ ID 22) with sequences SEQ ID NO 23-26.

5. Claims: 1-10,15,17-23,26,29,32-48 (all partially)

Same as invention 1, but directed at polypeptides of clone 5 (SEQ ID 27) with sequences SEQ ID NO 28-31.

6. Claims: 1-10,15,17-23,26,29,32-48 (all partially)

Same as invention 1, but directed at polypeptides of clone 6 (SEQ ID 32) with sequences SEQ ID NO 33-36.

7. Claims: 11-14,16,24,25,27,28,30,31 (all completely), 1-10, 15,17-23,26,29,32-48 (all partially)

Same as invention 1, but directed at polypeptides of clone 7 (SEQ ID 37) with sequences SEQ ID NO 38-41.

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/CA 99/00114

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9818931 A	07-05-1998	AU 5194598 A	22-05-1998
		AU 6909098 A	22-05-1998
		EP 0942983 A	22-09-1999
		EP 0941335 A	15-09-1999
		WO 9818930 A	07-05-1998
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